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DISSECTING ANEURYSMS *

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INTRODUCTION

The first description of a dissecting aneurysm is usually accredited to Laennec in 1826, but Peacock states that Mannoir recognized the lesion in 1802. The condition was certainly not generally appreciated until Laennec's publication, and since this time an extensive literature has grown around the subject. In 1925 Resnik and Keefer found 300 cases reported in the literature up to that time.

The pathogenesis of dissecting aneurysms is still in dispute and the conception of the mechanism of their formation has undergone a gradual evolution. The earlier authors were divided into two schools. The first thought that trauma to the vessel (high blood pressure) was the essential factor, with or without a pathological process in the coats of the vessel. The second considered disease of the intima to be of paramount importance with high blood pressure as a secondary agent. Later, attention was centered on changes in the medial coat, but the nature of these changes and the mechanism of rupture were debated, although the majority of authors agreed that intimal rupture was produced by high blood pressure acting in the presence of a weakened media. Within recent years a few individuals have stated that in some instances the medial changes cause hemorrhage into the aortic wall from the vasa vasorum, with secondary rupture of the intima.

The commencement of dissecting aneurysms is practically limited to the aorta, its branches being involved secondarily. Loeschke,

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however, found instances reported of primary dissecting aneurysms involving the pulmonary, lineal, thyroid and the cerebral arteries.

In a vast majority of cases the intima is lacerated at some point. The tear is most often located in the ascending portion of the aorta. Secondary rupture is frequent and usually occurs through the adventitia. Depending upon what portion of the adventitia is perforated there is hemorrhage into the pericardial sac, mediastinum or pleura. Sometimes the adventitia is ruptured in several places with the production of multiple hemorrhagic phenomena. Secondary rupture back into the lumen of the aorta has been observed in a number of cases, but this is relatively infrequent. The extent to which the aorta may be involved by the aneurysm varies from a few centimeters at one side of the base to complete separation of the coats throughout the circumference and length of the vessel, with extension down the iliac arteries. It is in this extensive type that reperforation into the lumen of the aorta is most frequently seen. In these extensive processes the large branches at the arch of the aorta and in the abdominal portion may be involved to a varying extent. The intercostal and lumbar vessels are frequently torn across or may remain intact and traverse the aneurysm. The clinical manifestations of a blockage of the aortic branches have been stressed by Crowell.

The fate of those suffering from dissecting aneurysms is usually death by hemorrhage, as indicated above. Occasionally the aneurysms which have a double opening from the aorta "heal." That is, the aneurysmal tube becomes endothelialized with the formation of a double aorta (Hall, Bostroem, Rindfleisch, Cleland, Adami, MacCallum, etc.). This is, of course, a rarity, some fifty cases having been found by Resnik and Keefer in 1925.

Laennec considered atheromatous change of the intima and its primary rupture to be the cause of the disease. Peacock attempted to produce dissecting aneurysms by injecting water into the aorta of cadavers. He found that the lesion could not be produced in normal aortas simply by heightened pressure in the vessel lumen. When the intima was damaged, however, dissection occurred if the rent in the intima was transverse to the long axis of the vessel. He concluded that a dissecting aneurysm could not be produced in a healthy vessel. In his cases of dissecting aneurysm Rokitansky, in 1852, found two distinct types of alteration in the vessel. In one the adventitia was

thickened, abnormally vascular and more easily separated from the media. In the other instance degenerative changes were present in the media. This coat was brittle and separated easily from the adventitia.

Since Rokitansky most authors have emphasized the medial changes as being of paramount importance, although nearly all agree that high blood pressure and primary rupture of the intima are essential factors in the actual production of the aneurysm. A wide variety of changes has been described. Thus von Recklinghausen observed minute tears in the media not associated directly with the aneurysm, and thought that the dissection occurred because of invisible (molecular) alterations in the physical properties of the tissue. Bostroem concluded that trauma is the most important factor in the production of dissecting aneurysms whether disease of the media is present or not. Degeneration of all the elements of the media in a 20 year old man was observed by Brouardel and Vibert. Degenerative changes in the media, unassociated with the disease process in the intima, were observed by Voigts. These changes involved particularly the elastic lamellae.

Lebert was the first to find inflammatory changes in the aorta associated with dissecting aneurysms. He found mononuclear infiltration and new-formed connective tissue cells in the adventitia and outer media. The elastic lamellae were destroyed and the vessel wall was weakened. Inflammatory medial changes also were observed by Lüttich but in his case the intima was markedly thickened while the media was atrophic, and this author concluded that dissecting aneurysms result from the intimal changes. Manchot found similar medial changes but concluded that they were secondary to the aneurysm and that laceration of the medial elastic fibers was the primary cause of the disease.

Inflammatory overgrowth of the muscle cells and areas of necrosis in the media were observed by Tschermak. The necrotic areas resulted in progressive thinning and final rupture of the elastica. In addition to these changes, new vessel formation and round cell infiltration were present. The whole length of the aorta was involved, but the lesion was particularly pronounced at the arch. This author applied the term mesarteritis to the condition.

Babes and Mironescu found moderate cell and vessel proliferation followed by minute hemorrhages, all the changes being confined to

the media. These processes caused the layers of the media to separate more readily and it is their contention that this increased separability is a necessary forerunner of dissecting aneurysms. Moriani also observed minute hemorrhages from the vasa vasorum in the media which he thought coalesced and caused the dissecting aneurysm. He also found fatty and hyaline changes in the media resulting in an increased separability of the medial fibers and concluded that medial rupture preceded the intimal tear.

Shennan and Pirie concluded that dissecting aneurysms are caused by vessel changes of two types. In the first the rupture is due to the presence of intimal atheromata. This type of aneurysm is limited in extent since it early breaks through the adventitia and results in death. The second variety is due to pathological changes in the middle and outer thirds of the media. The elastic strands are fragmented and more friable and, due to their rupture, small rents are produced which are filled with homogeneous material. The connective tissue is more abundant and shows hyaline and fatty changes. The muscle tissue is atrophic and decreased in amount. In the adventitia the alterations are not marked although there is an increased amount of connective tissue. The vasa vasorum are thickened and have either mononuclear or polymorphonuclear cells about them. These authors concluded that in this type of dissecting aneurysm the primary rupture is of the media, followed by the intimal tear.

In one case Krukenberg found three dissecting aneurysms, one extending the whole length of the aorta and starting from an intimal tear at the mouth of the innominate artery. The others were in the right and left inferior thyroid arteries, in one of which the intima was intact throughout. This author found inflammatory changes in the media similar to those marked by Babes and Mironescu and believed that in some dissecting aneurysms the medial changes are of primary importance. He pointed out that a tear in the intima is not necessarily an essential feature of dissecting aneurysms and held that in those cases in which the intima is intact the aneurysm undoubtedly arises from rupture of the vasa vasorum. He also believed, with Shennan and Pirie, that in the type of dissecting aneurysm which arises from the vasa vasorum the intimal tear is secondary to the production of the dissecting aneurysm and occurs through an atheromatous patch, as do all reperforations of such aneurysms into the vessel lumen.

Whitman and Stein reported a case where the medial layers of the aorta were split apart and a collection of clear fluid filled the defect. The intima of the vessel was intact. These authors laid great stress on the medial changes they found which were similar to those described by Babes and Mironescu and by Krukenberg.

Bay's case was remarkable because of a great decrease in the amount of elastic tissue of the aorta with increased brittleness of the vessel, which suggested to him the presence of a special disease process. This observer pointed out that whereas syphilis and arteriosclerosis may be causative in some instances, the occurrence of dissecting aneurysms in young people (boy of 8 years — Rokitansky) shows that these processes are not the only agents. Bay believes that raised blood pressure and blood vessel changes involving principally the elastica are necessary factors. He also pointed out the frequency of chronic nephritis concurrently with dissecting aneurysms.

Von Schnurbein stated that the underlying cause of dissecting aneurysms is Thoma's disease of the vessel and that the split occurs at the point of deepest penetration of the vasa vasorum into the vessel wall.

One case was presented by Loeschke where an undoubted gumma was present. He stated that syphilis is an unlikely cause unless definite necrosis is present.

Uniform changes were found by Lifvendahl in three cases. These consisted of an intimal tear at the base of the aorta, high blood pressure, renal arteriosclerosis and syphilitic mesaortitis. In one case a rheumatic vascular lesion could not be excluded. The syphilitic process was always most marked at the site of the intimal tear. This investigator reported the finding of syphilitic mesaortitis in one case each by Uhles and by Gsell, and the finding of renal arteriosclerosis in conjunction with dissecting aneurysms by Oppenheim, Busse and Loeffler. He stated that dissecting aneurysms occurred during labor in five cases cited by Bohmen.

Case Reports

Case 1. *Clinical History:* The patient, a white female, had never been a robust individual. In childhood she had measles, whooping cough and pneumonia. Since puberty severe frontal headaches occurred with each menstrual period. At the age of 31 the left breast was removed because of the presence of a benign tumor. At 46 years of age the patient entered the New Haven Hospital for a tonsillectomy and at this time the history of weakness and blurred vision,

together with the findings of a high blood pressure and failure to concentrate the urine, pointed toward renal disease, and a diet was prescribed. From this time on the patient was seen at frequent intervals on the Medical Service of the New Haven Hospital. On her first visit she had a slightly elevated blood non-protein-nitrogen, a blood pressure of 230/148 and a decreased phthalein output. The urine showed a trace of albumin and the specific gravity varied between 1.005 and 1.010. Early nephritic retinitis was present. During the next five years the patient was admitted to the New Haven Hospital seven times. The blood pressure remained above 200 systolic and the retinal lesions progressed so that central vision in both eyes was lost. At the age of 49, two years before her death, the signs of cardiac failure became manifest and from then on frequent digitalization was necessary. The final admission was at the age of 51 when she presented herself for digitalization. At this time the blood pressure was 265/140, cardiac hypertrophy was pronounced and the eye grounds showed extreme changes. The non-protein-nitrogen of the blood had reached 76 mg. per 100 cc. The blood Wassermann was negative, as it had been throughout her course. Digitalization was only partially successful and eleven days after admission she suddenly experienced difficulty of speech and in a few minutes had a complete right-sided hemiplegia. Consciousness was retained. The blood pressure rose to 295 systolic and the apex impulse of the heart was forceful. About forty minutes after the onset of paralysis she suddenly became cyanotic and in a minute or two was unconscious and gasping for breath. The apex beat and pulse at this juncture were impalpable and the heart sounds were inaudible. In another minute the heart stopped beating and the respirations ceased after a few more gasps.

Pathological Observations: The body weighed 60 Kg. and measured 166 cm. in length. The pericardial sac was distended with 425 cc. of clotted and fluid blood. The epicardium over the base of the aorta was lifted up by an accumulation of clotted blood. The base of the aorta was encircled by this hemorrhagic process which also extended up the aorta as high as the attachment of the epicardium, where it stopped abruptly in its upward course. The subepicardial hemorrhage extended laterally from the aorta to encircle the pulmonary artery. The reflection of the epicardium on the pulmonary artery was broken through, and the blood had extravasated into the loose tissue around the pulmonary artery and its branches to the hilum of each lung, and also extended anterior to the trachea over the arch of the aorta and along this vessel for a distance of 10 cm. beyond the origin of the left common carotid artery. The intimal lining of the thoracic division of the aorta showed slight atheromatous changes, there being a few yellow plaques scattered along this portion of the vessel. The vessel, however, was inelastic and brittle. The abdominal portion showed advanced atheromatous changes and some calcium deposition. The intima bulged inward at

the base of the aorta on the left, but the lining was intact throughout the entire vessel. After multiple cross-sections had been made to include the aorta, pulmonary artery and the base of the heart it was found that there was a large hemorrhage in the wall of the aorta which had split apart the fibers of the middle and outer thirds of the media and caused the inward bulging of the intima. The hemorrhage began 1.5 cm. above the aortic cusps and extended to within 1.5 cm. of the innominate artery. Above the aortic valve the hemorrhage half encircled the aorta but tapered to a point at its upper limit. Four centimeters above the aortic cusps the outer third of the media and the adventitia had ruptured and allowed the hemorrhage to extend beneath the epicardium on the base of the aorta. Two small tears were found in the epicardium behind the right auricular appendage. These tears permitted the development of the hemopericardium.

The heart weighed 675 gm. The right ventricle measured 6 mm. in thickness while the left measured 20 mm. The papillary muscles and trabeculae carnae of the right ventricle were flattened. Each kidney weighed 52 gm. and each showed the nodular, scarred surface associated with arteriosclerotic change.

The cerebral arteries showed advanced sclerotic changes and a massive hemorrhage practically replaced the left cerebral hemisphere.

Microscopic preparations of the ascending portion of the aorta showed that the middle and outer thirds of the media were split apart by hemorrhage. Red blood cells were packed between the medial fibers immediately surrounding the hemorrhagic area. There was no exudate present, however, and no evidence of necrosis, although some of the fibers stained less intensely than those further removed from the aneurysm. The adventitia was denser than usual and this layer and the subepicardial tissue over the base of the heart were packed with red blood cells which showed a typical thrombotic structure in many areas. The intima was slightly thickened and its lamellated structure had been replaced by accumulations of mononuclear leucocytes and amorphous material typical of early atheromata. The most striking changes were found in the vasa vasorum. In the adventitia and outer third of the media most of these vessels had undergone intimal proliferation which was so extensive in some cases that the lumen was entirely obliterated, while in others a mere

slit remained. In the outer media numerous vessels which did not show proliferative changes had a broad zone of hemorrhage about them, splitting apart the medial fibers. Many of these vessels were unassociated with the aneurysm but others were seen to lead into it. Occasional areas of perivascular fibrosis were encountered and sometimes the scarring dipped in from the adventitia. A few vessels had a narrow cuff of mononuclear leucocytes about them. Throughout the media, but particularly in the inner two-thirds, the collagenous tissue was increased in amount and appeared to replace the muscle fibers. The elastic lamellae were not decreased in number. They showed some fragmentation, but the most characteristic change was an irregular broadening out of the strands so that the fibers had a jagged appearance with an ill-defined border. Fat was abundant and was most plentiful in the inner third of the media. Minute fat droplets were present in the central part of the media adjacent to elastic lamellae, apparently replacing muscle tissue.

Comment: The patient had had definite and progressive renal disease for at least five years. The blood pressure during this time had been constantly elevated, usually above 200 mg. of mercury. At autopsy advanced generalized arteriosclerosis with particular involvement of the renal and cerebral vessels was present and the heart was greatly hypertrophied. Evidence of syphilitic mesaortitis was lacking, but the vasa vasorum at the base of the heart showed marked intimal proliferation. Many vasa vasorum were completely obliterated while others were thickened. Some were torn and had a zone of hemorrhage about them. Arteriosclerotic changes in the intima of the aorta were slight, whereas the media showed advanced degenerative changes. The hemorrahge was confined to the medial and adventitial coats and was apparently a terminal event owing to the early development of hemopericardium.

CASE 2. *Clinical History:* A white woman of 45 years was brought to the Accident Room of the New Haven Hospital with a diagnosis of perforated gastric ulcer. She had had influenza in 1918. Six years before admission she began having intermittent attacks of pain in both legs which forced her to remain in bed for four to five days at a time. For the past two years occasional attacks of paroxysmal dyspnea had been present. The seizures lasted about one-half hour. She had had dyspnea on exertion for many years and recently there had been some edema of the ankles. On the day before admission to the hospital she had fainted after slight exertion. She regained consciousness in about ten minutes and vomited a small amount of green material. She was brought to the hospital the next morning, having been suffering with great pre-

cordial pain and increasing dyspnea throughout the night. On admission the temperature was 101° F., the pulse was 100 and the respirations 32 per minute. The blood pressure was 140/80. Cyanosis was marked. The heart was found to be greatly enlarged and signs of early consolidation were present at the base of the right lung. The liver was palpable five finger-breadths below the costal margin. The blood Wassermann was negative. Eight hours after admission the patient died suddenly while sitting up in bed. About twenty hours had elapsed since the onset of symptoms.

Pathological Observations: The body was obese and weighed 72 Kg. The important findings were limited to the thoracic contents. The pericardial sac was distended by an accumulation of about 350 cc. of clotted and fluid blood. At the base of the heart and aorta the epicardium was bulged out by an accumulation of recently clotted blood. With this clot the organ weighed 700 gm. Most of the increased weight was due to hypertrophy of the left ventricle, the walls of which measured 22 mm. in thickness, while the right ventricle was 3 mm. thick. None of the valves displayed noteworthy changes. Throughout the aorta the endothelial lining of the intima was intact. There were numerous yellow plaques present, none of which contained calcium. The sclerotic changes were particularly marked in the descending thoracic and abdominal portions where there were numerous plaques about the orifices of the vessels. Two centimeters above the opening of the right coronary artery was a deep puckering of the intima and to the left of this the intima appeared to be stripped up from the media. On section through the posterior wall of the aorta it was seen that the media was lacerated tranversely 3 cm. above the base of the aorta. The tear extended 2.5 cm. to the left of the intimal puckering described above. Extending upward from the laceration the intima was dissected away from the media for a distance of 4.5 cm. The space between these two layers was filled with clotted blood. Below the transverse tear the blood dissected its way between the media and adventitia. Just over the base of the aorta posteriorly there was a small perforation of the adventitia which allowed the blood to escape beneath the epicardium. The subepicardial space was bulged out with clotted blood over the base of the heart, extending as high as the pericardial reflection on the base of the aorta. The subepicardial hemorrhage extended between the aorta and pulmonary artery and surrounded the latter structure and its branches to the hilum of each lung. The mediastinal tissues around the tracheal bifurcation were infiltrated

with blood. The epicardium had two minute perforations in its anterior surface between the aorta and the right auricular appendage. This allowed the blood to escape into the pericardial sac. On section of the lungs it was found that the blood followed the branches of the pulmonary artery on each side for a considerable distance.

In the microscopic preparations the break in the media was found to be a horizontal slit with irregular edges. The space between the severed medial fibers was filled with blood and the free edges of the muscles and elastic bundles were rolled up. Red blood cells were packed between the separated fibers for a short distance around the laceration but no leucocytic exudate was present and, although the tissue at the edge of the tear was stained poorly, there was no definite evidence of necrosis. Distally the hemorrhage extended to the origin of the innominate artery and lay between the intima and media, the former coat being intact throughout. Near the heart the blood had dissected between the outer and middle thirds of the media. At the base of the heart the blood lay nearer the adventitia. At the attachment of the aorta to the heart the hemorrhage extended entirely beneath the adventitia. About 1 cm. above the base of the aorta the adventitia was broken through and the hemorrhage had spread out into the subepicardial tissue.

The base and ascending portions of the aortic wall showed marked degenerative changes. In the adventitia and outer media the vasa vasorum had greatly thickened walls, so that some of the vessels were entirely occluded, while others were nearly so. The media was greatly distorted, particularly in the first 8 to 10 cm. of the vessel. There was but little muscle tissue left. Much of it was replaced by irregular accumulations of an amorphous, blue-staining material histologically resembling mucus. Many of these areas contained fat droplets. The amount of collagenous tissue was increased. There was a great decrease in the number of elastic lamellae and those which remained were short and frayed. There were numerous irregular, clear spaces or rents in the media which frequently occurred in the neighborhood of the vasa vasorum. Between the base and arch of the aorta there were many vasa vasorum which had ruptured and allowed red blood cells to extravasate into the surrounding tissue. In a few instances a vessel was surrounded by a narrow band of mononuclear leucocytes. The intima presented a normal appearance except in a few places where there were atheromatous thicken-

ings. In the sections from other parts of the body there was marked intimal proliferation in the arterioles. There was slight passive congestion of the liver and a few vascular scars in each kidney.

Comments: In this case there was a dissecting aneurysm present in a woman of 45 years. The intima was intact throughout but the walls of the aorta were split apart by hemorrhage. The media showed marked degenerative changes. The vasa vasorum were thickened or obliterated. Many were torn, forming small intramural hemorrhages.

CASE 3. *Clinical History:* While talking to his employer the patient, a white male of 70 years, suddenly fell, sustaining a laceration in the occipital region. He was brought to the New Haven Hospital by ambulance and was unconscious upon arrival. He died before an examination could be made. It was ascertained from relatives that the patient had suffered from shortness of breath for the past six months and that he had tired easily. Four months before death he had consulted a physician, who, it is stated, found a totally irregular heart action and signs of cardiac failure. The blood Wassermann was negative at this time.

Pathological Observations: At autopsy, seven hours after death, the body was found to be well nourished and well developed. It weighed 63 Kg. and measured 163 cm. in length. The pericardial sac was distended by an accumulation of 500 cc. of clotted and fluid blood. The heart weighed 400 gm. The coronary arteries were tortuous, thickened and brittle. Numerous atheromatous plaques were present in the intima but the vessels were patent throughout. The heart valves showed no noteworthy changes. The subepicardial tissue over the base of the aorta and the pulmonary artery was distended with clotted blood. The hemorrhage extended along the branches of the pulmonary artery into the hilum of each lung. There was also considerable hemorrhage into the mediastinal tissue. One centimeter above the base of the aorta posteriorly there was a tear in the epicardium which allowed the blood to escape from the subepicardial space into the pericardial sac. There was a massive hemorrhage between the media and adventitia of the aorta which began at the attachment of the aorta to the heart and extended upward for a distance of 7 cm. beyond the origin of the left subclavian artery. The hemorrhage lay between the media and adventitia throughout most of its extent, but in a few places the middle and outer thirds of the media were split apart. These tears led into the adventitial coat. The intima throughout the entire aorta was involved in extensive atheromatous processes which produced discreet and confluent ele-

vations, some of which were calcified. Between the origins of the innominate and the left common carotid arteries there was an aneurysmal outpouching 2 cm. in diameter which was entirely filled by a firm, laminated thrombus. The wall which bounded the aneurysm was continuous with the aortic wall. The entire intimal lining of the aorta was intact throughout. Each kidney weighed 150 gm. and they both had finely granular surfaces. The pelvic fat was increased in amount. Arteriosclerosis was advanced throughout all the peripheral vessels.

Microscopically there was definite evidence of syphilitic mesaortitis. This reaction was most pronounced at the attachments of the aortic cusps and in the wall of the saccular aneurysm between the innominate and left carotid arteries. The lesion was active in these areas and was characterized by the presence of numerous capillaries and a heavy infiltration of mononuclear leucocytes. This reaction was present in the adventitia and media and in a few instances extended to the intima. There was considerable necrosis of the medial fibers in the region of the aneurysm and throughout the syphilitic zones there were large accumulations of yellow pigment indicative of old hemorrhage.

As in the preceding cases the vasa vasorum of the adventitia and outer media were partially or completely occluded by subintimal proliferation. Some of the vasa vasorum of the media were torn and red blood cells had extravasated about them. In the entire ascending portion of the aorta the elastic lamellae were swollen, fragmented and decreased in number. This was particularly noticeable in the areas which showed definite syphilitic changes. The muscular component of the media was largely replaced by collagenous tissue and it was noteworthy that the bundles did not run in definite rows but were irregular, giving a cross-hatched appearance to the sections. In some instances the medial fibers stained poorly, were free of nuclei and appeared necrotic. This reaction was seen as a sharply demarcated band which partially encircled the aorta in the outer and middle thirds of the media. It was seen most clearly in the region where the aneurysm had dissected the medial fibers apart. The intima was thickened and showed considerable atheromatous change. Sections of the kidneys demonstrated numerous thickened arterioles with scarred kidney substance alternating with hypertrophic changes in the unscarred portions.

Comment: The case was one of sudden death from hemopericardium in a 70 year old man with a six months' history of cardiac disease. The heart was hypertrophied and although no reading was obtained it is probable that the blood pressure was elevated. The dissecting aneurysm occurred almost entirely between the media and adventitia although the media was involved to some extent. Syphilitic mesaortitis was present and in addition advanced degenerative changes had taken place in the medial coat. As in the other cases the vasa vasorum were extensively diseased, some having decreased lumina while others were torn and had old and recent hemorrhage about them.

CASE 4. *Clinical History:* The patient was a white male of 54 years. He was brought to the New Haven Hospital in a semiconscious condition. Three hours before admission he had had a sudden sharp pain in the back and slight numbness of the left leg and arm. He was cyanotic and the skin was cold. Great difficulty in breathing was experienced and there was a marked sensation of precordial oppression. Six months before there had been a similar attack with headache, dizziness, cyanosis and numbness of the left leg. The attack lasted three days. At this time the patient's doctor told him that he had a high blood pressure.

On admission to the hospital the patient was semicomatose but coöperative. Extreme cyanosis of the face and neck was present, the neck veins were engorged and the respirations were slow and shallow. The pulse and blood pressure could not be obtained. The heart sounds were weak and distant. The deep reflexes were absent. The patient vomited twice. Twitching of the left arm was noted and death took place forty-five minutes after admission to the hospital and about three hours after the onset of the illness. The Wassermann taken shortly before death was 2 plus in the alcoholic and the cholesterinized antigens.

Pathological Observations: The body was well developed and well nourished, weighed 79 Kg. and measured 169 cm. in length. The pericardial sac contained 590 cc. of clotted and fluid blood under some pressure. The heart weighed 600 gm. The left ventricle averaged 20 mm. in thickness while the right averaged 8 mm. in thickness. The coronary arteries were not unusually tortuous and the vessel walls were not thickened. There was a tear in the intima of the aorta which began 1 cm. above the right posterior sinus of Valsalva and extended upward in a semicircle for 3 cm. to end on the anterior wall of the aorta. There was extensive hemorrhage in all three coats of the calcified vessel about the tear. There was an atheromatous ulcer 2 cm. in diameter near the mouth of the innominate artery. Otherwise the intima was free from such change.

There was a dissecting aneurysm which involved the entire length of the aorta from the base to the bifurcation. Throughout its length the aneurysm lay between the outer coats of the media. At the base of the aorta the entire vessel was encircled by the process, which gradually narrowed until at the arch about one-half of the circumference of the aorta was dissected. At the arch the aneurysm lay posteriorly, and this relation was continued to the bifurcation. Some of the intercostal and lumbar vessels were torn across at their origins while others were intact. There was extensive hemorrhage into the adventitia over the base and ascending portions of the aorta. This hemorrhage followed the pulmonary arteries to each lung and spread out into the mediastinal tissue. The adventitia was ruptured beneath the epicardial reflection on the base of the aorta and the subepicardial tissues were distended with blood. Between the right auricular appendage and the aorta there was a tear in the epicardium 3 mm. in length which evidently allowed the hemopericardium to develop.

Serial sections through the region of the intimal tear demonstrated that the dissection extended almost straight through the media to the adventitia. The medial coats were separated in their middle and outer thirds and this level of dissection was maintained almost constantly throughout the aorta. Around the edge of the intimal laceration the medial fibers were split and the spaces were infiltrated with red blood cells. Along the line of longitudinal dissection the medial fibers were rolled up and there was abundant hemorrhage between the medial fibers adjacent to the aneurysm. In the ascending portion and arch of the aorta the outer third of the media was broken through in many places, with resultant hemorrhage into the adventitia.

The most striking changes were in the vasa vasorum and the fibers of the medial coat. The vasa vasorum of both adventitia and media showed the same intimal proliferation and reduction in the size of the lumina as has been described in the previous cases. In the media many vasa vasorum were torn and had hemorrhages about them. There was no definite histological evidence of syphilitic mesaortitis.

Comment: The dissecting aneurysm occurred in a 54 year old man who had serological, but no definite histological evidence of syphilis. The most uniform changes in the aorta were seen in the vasa vasorum, many of which were thickened and obliterated while

others were torn, giving rise to intramural hemorrhage. The medial fibers showed advanced degenerative changes.

CASE 5. *Clinical History:* The patient was a hod-carrier, 49 years old, who, while at work, suddenly experienced severe substernal pain. He became dizzy, dyspneic and lost consciousness for a few minutes. He left work and when he reached home intense pain was present in the epigastrium, which radiated down the inner side of both thighs. A doctor was called who found that a flaccid paralysis of both legs was present and that there was a loss of sensation from the symphysis pubis to the feet. Large doses of morphine failed to relieve the pain. Cyanosis appeared and death occurred about four hours after the onset of symptoms.

Pathological Observations: The body was well developed and nourished, weighing 90.9 Kg. There were 50 cc. of bloody fluid in the peritoneal cavity. There were a few fibrous adhesions at both pulmonary apices and calcified nodules were present in the tracheal nodes. The parietal pericardium was infiltrated with dark red blood throughout its anterior surface. The pericardial vessels were clearly demarcated coursing through the hemorrhage. The pericardial sac contained 350 cc. of clotted and fluid blood. The pericardial reflection on the base of the great vessels was lifted up by an accumulation of blood which entirely surrounded these vessels as far as the arch of the aorta and along the pulmonary artery into the hilum of each lung. The angle of reflection of the epicardium on the aorta was broken through, allowing blood to infiltrate the pericardium and extend in the loose tissue to the arch of the aorta. There was a tear in the epicardium 0.5 cm. in length, situated between the aorta and pulmonary artery. This evidently permitted the development of the hemopericardium.

The heart and aorta were removed intact and fixed in 10 per cent formalin. The heart weighed 600 gm. The left ventricle was greatly hypertrophied. All valve structures were within normal limits. The aorta was opened along its anterior surface. It was seen that there was a separation of the coats of the vessel throughout its entire length. The separation occurred between the layers of the media. At the base of the aorta the separation encircled four-fifths of the circumference of the vessel. At the arch the vessel was split about two-thirds of the way around, and from the arch to the bifurcation one-half of the circumference was involved. The intercostal arteries were torn across as they traversed the aneurysmal sac. The proximal lumbar vessels were similarly affected. From the base of the

aorta to the arch the dissecting aneurysm was filled with clotted blood but from here on the aneurysmal walls were in close apposition. At the commencement of the aorta, just above the valve cusps, there was a 2.5 cm. tear in the intima which was transverse to the long axis of the vessel. The upper edge of the tear overhung the lower to a slight extent and both edges were ragged and injected. The intima, throughout the ascending and transverse portions of the aorta, was discolored a dark, diffuse red with some yellow, raised, atheromatous areas showing through. The mouths of the intercostal vessels showed a considerable amount of sclerotic change. Otherwise the intima was quite smooth. The entire vessel, however, was brittle and it was observed that the edges of the aneurysm could, by slight manipulation, be extended around the aorta.

Multiple cross-sections were made of the entire aorta. It was observed that 5 cm. above the base the outer third of the media and the entire adventitia were ruptured, allowing blood to dissect between the media and adventitia and also beneath the epicardium, leading to hemopericardium through rupture of the epicardium, as described above. The great vessels at the aortic arch were split for varying distances by the hemorrhage, the innominate artery being the most extensively involved.

Seen microscopically, the base of the aorta was greatly decreased in thickness and the tissue was distorted. The intima was apparently the least damaged layer, although here there was some hyaline change and in places there were partially disintegrated red blood cells between the strands of tissue. The decrease in thickness was at the expense of the media where the muscle fibers were broken and replaced by hyalinized connective tissue over wide areas. What scanty elastic tissue remained was broken and frayed. There were many large gaps in the medial tissue filled with homogeneous acellular material which stained blue in hematoxylin and eosin preparations. There were also many clear spaces in this part of the vessel which were empty and represented tears in the wall of the vessel. Sections across the tear at the base of the artery demonstrated that the tear proceeded in an almost straight line through the intima and inner media to the outer fifth of the media. Here the medial fibers and the adventitia were thrown into outward curving folds by the pressure of blood. In the loose, subepicardial tissue around this point there was a dense cellular reaction consisting of an infiltration

of endothelial leucocytes, lymphocytes and a few polymorphonuclear leucocytes. Fibroblastic activity was also present. The dissection proceeded up the aorta and gradually assumed a position between the middle and outer thirds of the media. This level was maintained constantly throughout the rest of the vessel. Throughout the aorta the media was extensively changed. The elastic tissue was decreased in amount; the muscle fibers were poorly developed and there were many areas composed of fibrous tissue. The vasa vasorum showed considerable intimal proliferation and reduction in size of their lumina. It was further observed that there was a reduction in the total number of vessels at the base of the aorta. Many vasa vasorum were surrounded by an infiltration of mononuclear leucocytes. There were but few instances of hemorrhage surrounding the vasa vasorum. The tissue adjoining the line of the dissecting aneurysm was not more extensively changed than the rest of the media.

Comment: A 48 year old laborer without history of previous heart disease died of a dissecting aneurysm extending the whole length of the aorta. A tear was present in the intima just above the aortic cusps. The most striking change was the degeneration of the medial coat at the base of the aorta. The vasa vasorum did not show the obliterative changes described in the previous cases and the intima was relatively free from disease. A heavy cellular infiltration was present in the adventitia over the base of the aorta and was most marked opposite the intimal tear.

Summary of Cases

In the five cases presented the oldest was 70 years of age, while the others ranged between 45 and 54 years of age. In the first four cases where adequate histories were obtained there is evidence of pre-existing cardiac disease, the duration varying from a few months to over two years. The onset of illness was characterized in all five instances by the sudden appearance of precordial pain or oppression, dyspnea and prostration. Loss of consciousness accompanied the onset in four individuals. In the fifth case the blood pressure was not determined but in the others a reading was taken either before or during the attack and was found to be high. The blood Wassermann was positive in one instance (Case 4). After the onset of symptoms death occurred at intervals varying from a few minutes to

twenty hours, and in all instances was due to hemopericardium. The lowest cardiac weight was 400 gm.; the rest of the hearts weighed 600 gm. or more. In three cases the intimal lining of the aorta was intact. Two were lacerated just above the aortic cusps. The aneurysm extended from the base to the arch in all but two cases and in these two the entire vessel was involved down to the bifurcation. The path of dissection of the aneurysm was nearly always between the middle and outer thirds of the media. Occasionally the plane lay between the media and adventitia but only for a short distance. Even in those cases where the intima was lacerated the tear proceeded straight through the media to its outer third before pursuing a longitudinal course. The pulmonary vessels and mediastinal tissues were infiltrated and in all cases the outer media and adventitia were ruptured at some point beneath the reflection of the pericardium on the base of the aorta. This led to the development of hemopericardium through perforation of the epicardial layer over the base of the heart.

The intimal lining of the thoracic portion of the aorta was surprisingly free from change in all but one case which showed numerous atheromata. Striking changes were observed in the media of all cases. Here degenerative processes were paramount and were particularly marked in the ascending portion. The muscle fibers were decreased in number, and fat and collagenous tissue replaced them. The elastic fibers were apparently fewer and many of those which remained were broken and frayed. In many instances there were broad zones where the medial tissue had lost its cellular outline and was apparently composed of hyalinized tissue. Jagged rents in the continuity of the media were of frequent occurrence. Small accumulations of material, histologically resembling mucus, were seen packed between the muscle and elastic fibers. Fat deposits as small droplets were present as far out as the outer third of the media.

The most pronounced and uniform change was in the vasa vasorum of the ascending aorta. In the adventitia and loose areolar tissue just outside this coat these vessels showed the most advanced intimal thickening, resulting in some instances in complete occlusion, while the lumen of others was reduced to a mere slit. In the outer half of the media, in addition to being thickened, many of the vasa vasorum were torn and had zones of hemorrhage about them. This process was noted at a distance from the path of the dissecting

aneurysm and also near the aneurysm and leading into it. In all cases many of the intact vasa vasorum had a cuff of mononuclear leucocytes about them. In one instance there was undoubted evidence of syphilitic mesaortitis and the process was fairly active.

Discussion

The outstanding feature of the cases reported here, and of many of those abstracted from the literature is the uniformity of the pathological process. The majority of cases occur in patients between 45 and 60 years of age, although the aorta is not markedly sclerosed in these individuals, as judged by the extent of intimal change. The entire vessel, however, is inelastic and brittle. As would be supposed from the blood pressure determinations, all the cases had hypertrophied hearts. The base of the aorta is first affected and is the portion most extensively involved by the aneurysm. The path of dissection followed by the aneurysm is constant with but a few minor variations, and the mechanism of death in each case is practically identical. The similarity is further emphasized by microscopic study of the aorta, when it is seen that the media, particularly at the commencement of the vessel, is the seat of advanced changes. These consist of degenerative processes which reach such a high degree that the media must be greatly weakened. The fact that in this series three of the dissecting aneurysms occurred without a break in the intimal lining does away with the common conception that an intimal tear is a necessary factor in the production of the disease. Also, in these cases the vasa vasorum obviously are the only possible source of the hemorrhage.

A plausible explanation of the mechanism for the rapid development of a dissecting aneurysm which is not in communication with the aortic lumen is sought. Owing to the weakened condition of the medial coat, plus the heightened blood pressure, one or more vasa vasorum rupture into the medial coat. The hemorrhage forms an intramural hematoma. The internal pressure in the aorta is exerted upon the hematoma and causes it to spread along the line of least resistance, *i. e.*, the media, since this is now the weakest coat and, as it has been demonstrated, its fibers are more easily separated. The intramural hemorrhage begins at the base of the aorta and attains its greatest size at this point, since it is here that the medial

changes are paramount. The highest pressure in the lumen of the aorta occurs at the base; therefore it is at this point that the adventitia finally gives away with the subsequent development of hemopericardium. Laceration of the intima must also be considered in the light of the foregoing discussion. The old statement that high blood pressure and an intimal tear, however produced, are necessary and sufficient factors for the production of a dissecting aneurysm is hardly tenable. It is more certain that medial degeneration is a prerequisite and it is probable that intimal laceration is secondary to the formation of the dissecting aneurysm in most, if not in all, cases.

There are several facts which bear out this point of view. In the first place the reasoning employed to explain the rupture of the adventitia would apply to tearing of the intima as well, since it is nearly always at the base of the aorta that the intima is lacerated. When other sites are chosen it is usually possible to find a deep atheromatous process extending into the media which would sufficiently weaken the intimal lining to allow perforation to occur from the aneurysm in the media through to the aortic lumen. Secondly, in the usual case with the intimal tear occurring just above the aortic cusps, the break proceeds straight through the vessel to the outer media and never strips up the intima. Furthermore, a third point to be considered is the fact that over the surface of the ordinary atheromatous ulcer the intimal lining is often deficient, yet no dissection of the vessel coats is observed around the ulcer. Finally, Gallavardin and Gravier observed a case where the intima was lacerated transversely just above the aortic cusps — the favorite site in dissecting aneurysms — and no dissection of the coats occurred. They state that the media was normal histologically.

Determining etiology from the study of histological sections is always dangerous and in searching for the underlying cause of the medial changes occurring in these cases one can go no further at present than the lesions observed in the vasa vasorum. The occlusion of large numbers of these vessels might easily so embarrass the blood supply of the media that degeneration of this coat would result.

The presence of syphilitic mesaortitis in one case substantiates, rather than vitiates the argument, since this disease notably attacks the vasa vasorum with resulting intimal proliferation, and also involves the media, with the production of necrosis in the active phase

and fibrosis late in the course. Syphilis as the chief cause of dissecting aneurysms is unlikely, since in a majority of the cases in the literature this lesion was absent and in four of the present series there was no evidence of the disease histologically.

A further possibility is suggested by Case 5. In this instance the vasa vasorum at the base of the aorta did not show the marked occlusive changes that would be expected from the high degree of degeneration observed in the media. In fact no vasa vasorum at all were visible over large areas. There was, however, a chronic inflammatory process in the subepicardial areolar tissue over the base of the aorta. This area coincided with the commencement of the aneurysm and it is possible that the inflammatory process had completely destroyed the vasa vasorum. This case would, therefore, represent a more advanced stage in the diminution of the vascularity of the aortic coats.

Conclusions

1. The development of a dissecting aneurysm of the aorta is apparently dependent upon degenerative changes in the medial coat.
2. The underlying cause of the medial change is probably obliteration of a large number of vasa vasorum from arteriosclerosis or a low grade inflammatory process.
3. The aneurysm begins by a rupture of one or more vasa vasorum into the weakened medial layer, with the formation of a hematoma which splits apart the medial fibers.
4. A tear in the intima of the aorta is not a necessary factor in the formation of a dissecting aneurysm.
5. When initmal tears do occur, they are probably secondary to the development of the aneurysm.

Note: The author wishes to express his thanks to Dr. Raymond Hussey for his interest in this work and for permission to publish the cases.

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DESCRIPTION OF PLATES

PLATE 125

FIG. 1. Dissecting aneurysm splitting apart the medial fibers on the posterior wall of the aorta. The inward bulging of the intima is due to a large hematoma in the media. Slight atheromatous change. The outer media has ruptured allowing blood to extravasate beneath the adventitia of the aorta and pulmonary artery. Drawing from Case 2.

1

PLATE 126

FIG. 2. Dissecting aneurysm between the middle and outer thirds of the media. The outer media of the aorta has ruptured, causing a massive subadventitial hemorrhage completely surrounding the base of the aorta and pulmonary artery. The intima shows advanced atheromatous changes but is intact. There is a syphilitic, saccular aneurysm between the innominate and left carotid arteries. The fibrous cord of the ductus arteriosus is present. Drawing from Case 3.

2

PLATE 127

FIG. 3. Dissecting aneurysm between the fibers of the media. The intima shows slight atheromatous change, but a laceration is present just above the aortic cusps. The outer media has ruptured, allowing blood to extravasate beneath the adventitia around the aorta and pulmonary artery to the hilum of each lung. Drawing from Case 4.

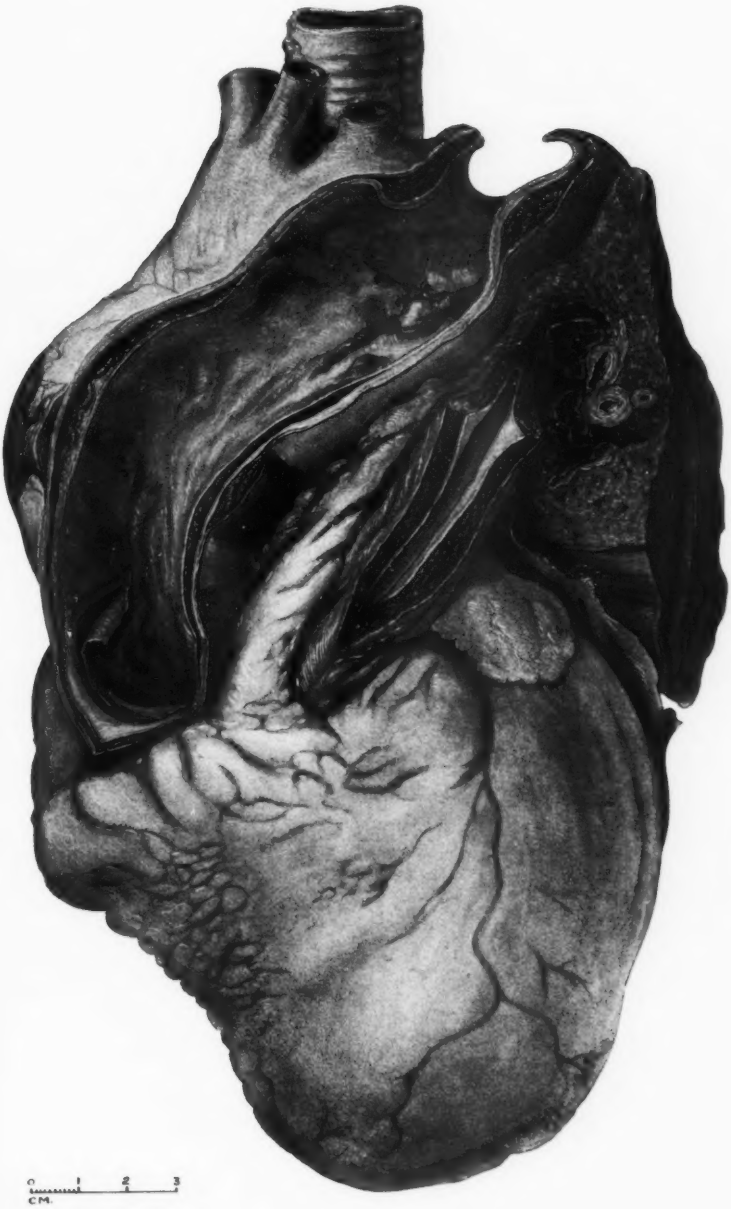

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PLATE 128

FIG. 4. Dissecting aneurysm extending the whole length of the aorta with a laceration of the intima just above the aortic cusps. The intimal lining is discolored by the blood outside it. Slight atheromatous change is present. The media has ruptured, allowing blood to extravasate beneath the adventitia. The adventitia has ruptured beneath the epicardium and this layer in turn has perforated at a point between the origins of the aorta and pulmonary arteries, causing hemopericardium. Drawing from Case 5.

4

PLATE 129

Cross-sections of the aortas from the cases described, showing the path of dissection of the aneurysm with hemorrhage in the tissue surrounding the aorta.

FIG. 5. At the level of the innominate artery. Case 5.

FIG. 6. At the level of the innominate artery. Case 4.

FIG. 7. At the level of the common carotid artery. Case 5.

FIG. 8. At the base of the heart. Showing rupture of outer third of media with hemorrhage beneath adventitia. Case 1.

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PLATE 130

FIG. 9. A section at the base of the aorta showing the laceration of the intima and media with splitting apart of the media and adventitia by hemorrhage. Case 5. Hematoxylin and eosin stain. × 20.

FIG. 10. Large vas vasis in the adventitia at the base of the aorta. Occlusive changes are marked and the lumen is represented by a mere pin-point opening. Case 2. Hematoxylin and eosin stain. × 85.

FIG. 11. Arteriole and vein in the outer media. The arteriole is nearly occluded by thickening of its wall. Massive hemorrhage is present in the adventitia. Case 1. Hematoxylin and eosin stain. × 100.

FIG. 12. Rupture of vas vasis of media with extravasation of red blood cells. Case 1. Hematoxylin and eosin stain. × 125.

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10

11

12

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PLATE 131

FIG. 13. Extravasation of red blood cells around vasa vasorum of media. Case 1. Hematoxylin and eosin stain. × 120.

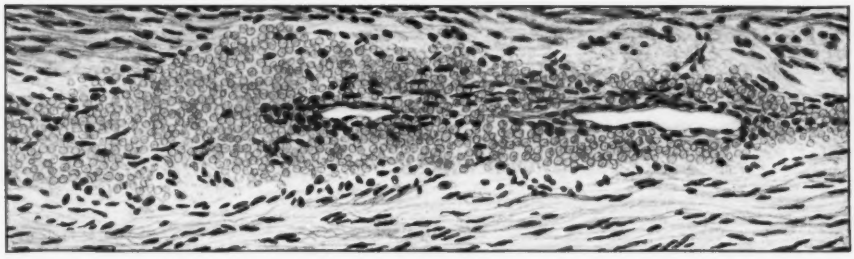
FIG. 14. Two thickened vasa vasorum deep in the media. Degenerative changes about them. Case 4. Hematoxylin and eosin stain. × 120.

FIG. 15. Syphilitic changes at base of aortic cusp. Mononuclear infiltration and new vessel formation. The dark spots are composed of changed blood pigment indicative of old hemorrhage. Case 3. Hematoxylin and eosin stain. × 120.

FIG. 16. Hemorrhage in media of aorta at the top of the picture. Large spaces or "rents" in media at bottom of picture. Loss of nuclear structure and hyalinized appearance of medial fibers. Case 4. Hematoxylin and eosin stain. × 120.

FIG. 17. Large irregular tear in media with marked retrograde changes in the medial fibers. Some small round cell infiltration is present. Case 3. Hematoxylin and eosin stain. × 50.

FIG. 18. Section completely through the aorta at the base. The entire wall of the vessel is thin and atrophic. The normal structure is absent. Most of the wall is occupied by large spaces filled with homogeneous blue-staining material. Only a few distorted muscle and connective tissue fibers remain. Case 5. Hematoxylin and eosin stain. × 50.



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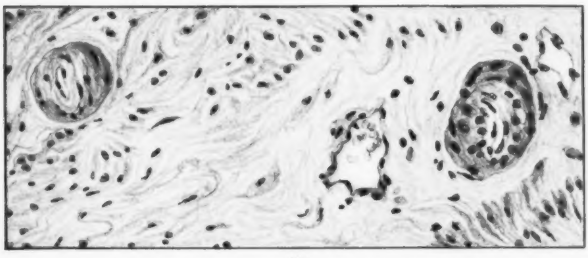

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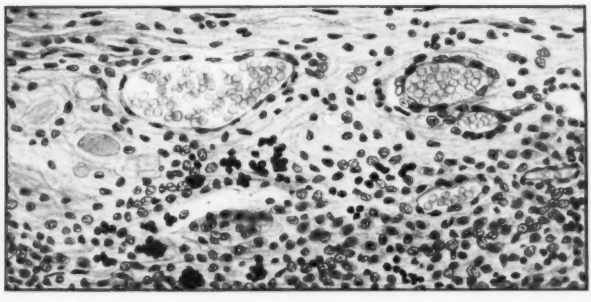

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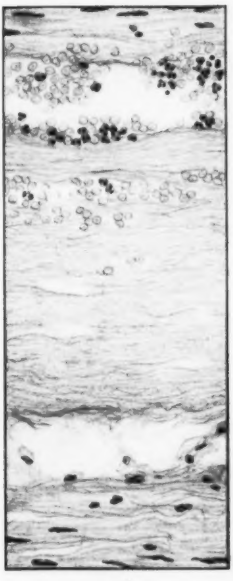

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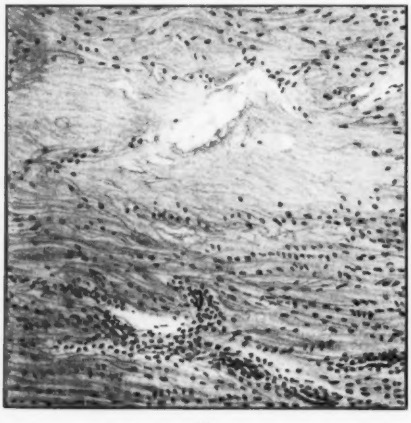

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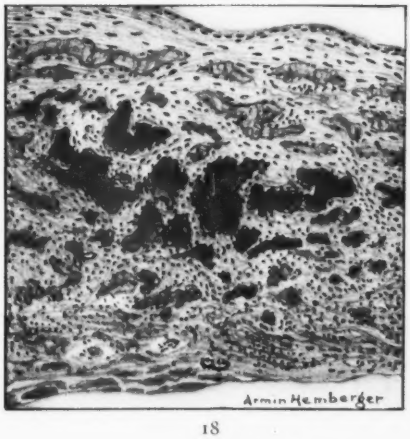

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Tyson

Dissecting Aneurysms

TWO CASES OF MELANOMA OF THE MENINGES WITH AUTOPSY *

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INTRODUCTION

Scarcely a dozen cases of primary melanoma of the meninges have been reported, so that the condition is by no means common and further details, accumulated from carefully studied material, should be of value, both as proof of the potential meningeal origin of this tumor and as evidence for the theory that melanoma is of nervous rather than of dermal origin.

That melanoma is of nervous origin and is closely related to neurofibroma was the thesis of an article by Soldan [1] in 1899. Masson [2, 3] resurrected this theory from the oblivion into which it had fallen when he wrote his excellent articles nearly thirty years later. He says that he had already come to his conclusions before discovering that Soldan had antedated him, but although he gives Soldan priority, the credit for putting the nervous origin of the nevi and melanomas on a firm and convincing basis, and for discovering their connection with tactile corpuscles, belongs wholly to Masson.

It is needless to cite all the literature on the subject; the reader will presumably be interested merely in knowing the recent developments in the matter. It is only today that Masson's articles, written five years ago, are beginning to bear fruit. In this country this is chiefly due to the fact that Ewing [4, 5] has recognized the merits of his claims and sponsored them in the latest edition of his book "Neoplastic Diseases," as well as in a brilliant paper in the *British Medical Journal*. In spite of this, however, the older views continue to flourish and we find Miescher [6] (who published a lengthy article on the dermal origin of melanoma about the same time that Masson's papers appeared) adhering to the dermal theory, although cognizant of Masson's work which he mentions as being praiseworthy, ingenious, but not proved.

* Received for publication June 21, 1931.

A monograph of 232 pages by Dawson,[7] which appeared two years prior to Miescher's article, should not be overlooked in a discussion of the melanomas. In this excellent paper, which is very profusely illustrated, Dawson considers every side of the question from all angles but one, the neurogenic, which was not brought into prominence until Masson rescued it from the discard. Dawson's point of view is, therefore, necessarily an epidermalistic one. In considering the tumors said to be primary in the nervous system, melanoma of the meninges, and so on (pp. 671–672), he expresses doubt as to their being true melanomas, but he discusses them with an open mind and refers to the literature that explains their origin on a chromaffine basis. For a complete review of the subject up to 1925, and as a source of reference material on melanoma (there are seven pages of bibliography), this article will be found to be invaluable: it is probably the most complete exposition of this topic in the English language, taking up the consideration from the historical, developmental, normal histological, pathological and clinical points of view, and presenting many valuable points in the way of classification.

Four origins have been assigned to the melanoma: skin, endothelium, connective tissue and the tactile corpuscles of Wagner-Meissner. The dermal and nervous origins have come into increasing prominence and we may neglect the others for the present. Masson's expansion of Soldan's theory is as follows: melanoma originates in the cells of the Wagner-Meissner corpuscles, in the more peripherally situated Merkel-Ranvier bodies, and in scattered cells of a similar nature embedded in the epidermis. All of these are situated along the course of sensory nerve endings, which are at first myelinated and lose their sheaths as they enter the cell groups of the corpuscles, to terminate in arborizing or reteform plexuses with varicose nodes around the epithelioid cells. Thus the nerve fibers and their cells play a part in these tumors, giving them a resemblance to neurofibromas. Building up this thesis Masson begins with the cell of the tactile apparatus as the type cell and derives therefrom two forms of benign tumor: (1) the superficial or quiescent nevus of the epidermis and (2) the deeply situated, pigmented nevus of the derma. From these the transition to the malignant forms ("melanosarcoma," "melanocarcinoma") is readily traced. The type cell has two potentialities: it may be non-pigmented and associated with

nerve endings, or it may be pigmented more or less deeply and apparently less intimately associated with them in that case. The first type is the "nevus cell," the second the "melanoblast." As proof of this theory Masson sets forth the following points: (1) these tumors have a readily demonstrable neurofibromatous substratum; (2) they have the structure of distorted Wagner-Meissner corpuscles; (3) with his trichrome stain he demonstrates medullated and non-medullated nerve fibers among the tumor cells and the marked similarity of these to those of the Wagner-Meissner and Merkel-Ranvier bodies, and (4) silver impregnation, which he admits was imperfectly carried out, bears out his ideas as to the presence of nerve fibers and filaments. The whole theory is beautifully presented and leaves little to be done in order to prove its validity, aside from carrying out more perfectly executed silver impregnations.

The melanoblast, which gives the tumor its name, Masson believes to be a phase of the type cell in which melanin metabolism plays the chief part; this, he thinks, is secondary and incidental. The branched or racquet-shaped melanoblasts are regularly intercalated in the basal cell layer of the epidermis and have given rise to the theory of basal cell origin of the melanomas. They are also known as "Langerhans cells." Their histogenesis has long been a topic of lively dispute. Whatever it may be, Masson remarks: "Les cellules de Langerhans sont" — they exist. The pigmented melanophores of the derma he believes to be ordinary histiocytes that have taken up melanin dropped by the melanoblasts.

The "epidermalist" school, typified by Bloch and Miescher, explain the tumor as follows. Somewhat naïvely orienting their theory to the conventional microscopic section of skin, with the epidermis at the top and the derma at the bottom, they speak of a loosening of the basal cells, with a dropping-down ("Abtropfen") into the derma in plugs or columns in the manner of stalactites, or scattered discretely. This theory is quite familiar to us all. Accordingly as the origin of these pigmented basal cells is assigned to epidermis, connective tissue, or adventitia, we derive three of the four histogenic theories. The epidermalist recognizes at once the fact that the type cell differs from the epidermal cell in several respects: it is clear, not cloudy; it lacks intercellular bridges or "prickles"; it has no intracellular fibers and it differentiates into two types of cell in the tumor. To explain this he must postulate that the cell rounds up, loses its

prickles and fibrils and becomes associated with its fellows into cell nests that are quite unlike epidermis. Unfortunately, as Ewing points out, the unquestionable association of epidermal proliferation with the production of nevi and melanomas (also seen in other subepidermal conditions), the questionable histogenesis of the Langerhans melanoblast and the occasional presence of epidermal "pearls" in melanomas, all appear to bear out this process of reasoning. In this theory no account is taken of the nervous framework of the tumor, the nerve endings in the cell nests, the proliferation of myelinated nerve fibers near the base of the tumor, or of the presence of the small, lymphocytoid cells that Masson interprets as cells of the sheath of Schwann — all of which he points out in detail. This is due to the fact that stains have been employed which fail to bring out most of these details. Masson stresses the futility of attempting to rely on the routine stains in this connection, in an appendix to his second article.

Which of these two theories puts the least strain on one's imagination? Is it easier to accept the elaborate anaplasia and subsequent metaplasia of the epidermalists' theory, or the straightforward, systematic derivation of the tumor from wayward nervous elements of the tactile apparatus, as advanced by Soldan, Masson and Ewing?

In this paper, it will be our purpose to describe two cases in which melanomas originated in the meninges and not in the skin, to report the results of a careful study of these tumors by means of a very varied technique and to endeavor to adduce therefrom further proof as to the validity of the theory of nervous origin of melanoma. There is no evidence in either of our cases of the existence of pigmented tumors in the skin or the eye. We admit in advance that such tumors may have been present, but as none was noted at autopsy, or in the clinical histories, this seems improbable. Cerebral symptoms dominated the picture in both instances, the eyegrounds were examined in both and nothing was found, aside from choked discs in one case. That melanoma can and does arise from the meninges is accepted by the best authorities. In that case, how could it arise from epidermal cells? One would have to postulate all sorts of unlikely possibilities: inclusion, fetal rests and the like. In support of the neurogenic origin of such growths we have the statement of histologists, Maximow among them, that many meningeal

nerves end in organs quite similar to the Wagner-Meissner corpuscles. What more could the proponents of this theory desire?

In our cases, then, we must show the complete similarity between our meningeal tumors and ordinary epidermal melanomas and we should prove the absence of skin or ocular lesions. The former we can do; the latter we can assume for the reasons already given: to the best of our knowledge and belief no such tumors were present.

Report of Cases

Case 1. *Clinical History:* A white male, about 40 years of age, was admitted to the hospital complaining of severe headache that had been intermittent, with gradually increasing intensity since its sudden onset about one month before. The pain was most severe over the vertex. About two weeks prior to admission projectile vomiting, unassociated with nausea, followed eating. The patient's wife had noticed a change in his character during the last few weeks, which she described as "sort of delirium with increasing irritability and carelessness in personal habits." For the last three years the patient had been a diabetic, the disease being under dietary control. His past and family history were irrelevant to the present illness.

Physical examination revealed a well developed, well nourished man, disoriented as to time and space and showing slow cerebration. There was marked exophthalmos, but the pupils and fundi were normal. The right drum membrane was slightly congested, but not bulging. The knee jerks and Achilles' reflexes were absent; Brudzinski's and Kernig's signs were positive. All other physical signs were irrelevant. The spinal fluid was bloody, under increased pressure, with positive globulin, negative Wassermann and only fourteen cells. Clinical and chemical blood tests were negative, save for a white count of 10,800 and a blood sugar of 130 mg. Temperature was 99 F, blood pressure, respiration and pulse rate essentially normal.

The patient was under observation and treatment in the hospital for eighteen days before his death, during which time his left leg became spastic, ataxic and finally weak. There was increasing drowsiness with decreasing ability to coordinate and to cerebrate, dysphagia and dysphasia developed and finally stupor supervened, the extremities became weak and cyanotic and the patient died about seven weeks after the onset of symptoms. No definite diagnosis was made before death: the impression was hemorrhagic encephalitis.

Autopsy: Three hours postmortem. The body and extremities were essentially normal externally and internally, with the following exceptions: there was an early lobular pneumonia, congestion of the abdominal viscera and moderate obesity.

When the meninges were exposed, numerous small, smut-colored nodules were seen to be scattered through all portions of the pia arachnoid of both brain and cord. They varied from pin-point to 3 mm. in size and were most numerous over the frontal lobes, the

brain stem and the fissure of Sylvius. On attempting to strip the pia from the brain, some of these nodules were found to extend into the cortex for a distance of several millimeters and were inseparably connected with the brain tissue. Most of them were flat and barely palpable, and in the gross they appeared much like old petechial hemorrhages. The cerebral convolutions were markedly flattened. On sectioning the brain, a dark red mass, about 2.5 cm. in diameter, was found in the area just above the quadrigeminal plate, apparently obstructing the aqueduct of Sylvius and connected with the meninges and choroid plexus in this region. The third and lateral ventricles were dilated, and minute discolored areas, somewhat similar to those in the meninges, were found on their walls.

Microscopic Examination: Routine examination of sections from the brain and cord revealed tumors, apparently originating in the mass in the neighborhood of the choroid plexus and third ventricle (which was the only sizable growth found), or arising in a multiple fashion. They were composed of closely packed ovoid cells that frequently contained melanin and were more or less perithelial in their grouping. They were not unlike the usual acinar "melanocarcinoma" in their appearance. Usually superficial in the meninges, they sometimes invaded the cortex, particularly in the case of the cerebellum which showed columns of tumor cells penetrating quite deeply into its substance. The pigment was examined for iron, lipins and melanin, and the tests proved it to be the last. Reticulum stains showed a copious reticular network in the tumor and its metastases, the fibrils being apparently derived from the meninges.

CASE 2. *Clinical History:* White male, 45 years of age. The patient was admitted to the hospital in delirium and rapidly lapsed into coma. The only history obtainable was that he had complained to his family physician of headache, dizziness and vomiting six weeks prior to admission. A complete neurological examination was not made at the time. Three weeks later, following the extraction of several teeth, his symptoms became more pronounced and whenever he attempted to walk, he staggered toward the right. Two days before admission he became delirious.

Physical examination showed a well developed, well nourished, unconscious man whose heart, lungs, abdomen and extremities were essentially unremarkable except for the following reactions: Brudzinski's positive bilaterally; abdominal negative; triceps questionable; cremasteric positive only on the right; Babinski's, Oppenheim's and Gordon's present bilaterally; contralateral Gordon and Oppenheim on the left; Kernig's positive bilaterally. The ocular fundi showed markedly choked discs, but were otherwise normal. There was cervical rigidity. The spinal fluid was clear, but under increased pressure. The white count was 21,000, the temperature 98 F. All other findings were negative. It

was believed that the patient had either a brain abscess or tumor; therefore an exploratory craniotomy was done and a needle inserted into several areas of the right cerebral hemisphere in the hope of locating an abscess, a cyst, or a tumor, but without success. The patient died suddenly the next day.

Autopsy: Six hours postmortem. External examination revealed nothing save the surgical wound, an old, healed right rectus scar and the evidence of recent tooth extractions. On opening the peritoneal cavity, dense fibrous adhesions were found at the site of a former appendectomy. The heart and aorta showed nothing but a moderate atheromatous degeneration of the latter. The spleen, liver, gastro-enteric tract, pancreas and genito-urinary tract were all essentially normal. The lungs weighed 530 gm. right, and 350 gm. left. Scattered throughout all their lobes were small, irregularly shaped, lobulated nodules of firm, grayish white tissue (about twelve in all) and varying from 2 to 20 mm. in diameter (Fig. 1). These were situated just beneath the pleura and one of them was at the center of a dark red, wedge-shaped area of infarction. Although the large pulmonary vessels were free from emboli, the smaller ones near some of the subpleural nodules were plugged with dry, grayish red material resembling ante mortem clot. The lung tissue not involved in the lesions just described was crepitant and dry. The hilic lymph nodes were not remarkable excepting for one, in which there was some grayish white tissue closely resembling the subpleural nodules and which was slightly larger than its fellows.

When the calvarium was removed very little blood clot was found at the operative site, the meninges were tense and there was marked flattening of the convolutions, particularly on the right. Horizontal sections revealed two large nodules of abnormal tissue in the right cerebral hemisphere (Fig. 2). The larger measured 3 by 2.5 cm. and was situated in the anterosuperior portion of the temporal lobe just posterior to the Sylvian fissure. It was well demarcated from the surrounding brain tissue and could be easily shelled out of its bed, except at one point anteriorly, where it was in contact with, and apparently attached to the meninges of the Sylvian fissure. The cortex could be seen to be pushed aside and to have undergone pressure atrophy in the neighborhood of the nodule. At the center of the mass was considerable hemorrhage and softening. The smaller nodule was spherical and measured 2 cm. in diameter; it was situated in the anterior central gyrus, lying between the fissure of Rolando and the precentral sulcus. It was in contact with the meninges ex-

ternally and in the fissure of Rolando. There was little hemorrhage into this nodule and it appeared to be a younger growth than the larger one in the temporal lobe. The brain tissue of the right cerebral hemisphere showed evidence of compression and there was almost complete collapse of the right lateral ventricle. No other pathological changes were observed in the brain. On account of the fact that brain tumors do not ordinarily metastasize to the lungs, all the viscera, as well as the external surface of the body and its internal membranes, were examined a second time for a possible primary focus, but none was found.

Microscopic Examination: This revealed the brain tumors to be exactly similar to one another (Fig. 3). They were composed of solid nests of ovoid cells with a delicate nucleus, prominent nucleolus and clear to cloudy or granular cytoplasm. In this case also, as in Case 1, the perithelial grouping was striking. It was only after having discovered melanin in some of the cells of the lung tumors that we went back and found a few melanotic cells in the brain nodules. They were essentially amelanotic in appearance, until silver impregnation picked out many latent melanin granules (Fig. 4). A reticulum impregnation revealed copious reticulum in the larger brain tumor, scanty reticulum in the smaller, similar in its arrangement to that seen in Case 1. The lung metastases, for we must consider them as such, showed essentially the same picture. They differed in that there was more melanin, although it was scanty at best, and found only in certain areas of the slides. A further difference was a tendency for the tumor cells to form hollow acini, quite similar to those of an adenocarcinoma, between which aberrant cells were scattered in the dense reticular stroma. With the Morgan-Weigert iron-hematoxylin method it was seen that the cells lining these acini often projected quite to the middle and formed a rosette-like body with their "tails" radiating toward the center. In other places the cells were layered and more or less concentrically arranged, as in the Wagner-Meissner corpuscles; in fact, the resemblance of some of the pulmonary tumor acini to these structures was very striking.

Special Stains and Impregnations

Rather than go into the structure of the tumor any further, from the standpoint of ordinary methods of staining, it would be better to detail some new pointers toward its nervous origin. Reasoning that

Masson had purposely somewhat neglected the silver impregnations and that a method derived from Cajal and Bielschowsky traditions by Foot [8] had always demonstrated nerve fibrils very well, we subjected frozen sections of the tumor to this treatment and obtained the striking results shown in our illustrations. The method is as follows:

Silver Impregnation of Tumor Fibrils: Fixation in 10 per cent neutral formalin, frozen sections at 20 microns. Place sections in equal parts of pyridin and absolute alcohol for 30 minutes and transfer to pure pyridin for from 3 to 10 hours. Wash out the pyridin in several changes of water and transfer to distilled water. Impregnate for one-half to one hour in the ammoniacal silver solution (silver diammino hydroxid) devised by Kubie and Davidson,[9] which is prepared as follows:

To 10 cc. of 10.2 per cent silver nitrate add strong ammonia drop by drop until the resulting precipitate is just dissolved. Add 10 cc. of 3.1 per cent sodium hydroxid and dissolve the resulting reprecipitation in just enough strong ammonia, added dropwise, to clear the solution. Do not add more ammonia than is needed. Make up to 100 cc. with distilled water and heat to 45 C.

After the sections have been impregnated in a closed vessel (to prevent precipitate which results in open dishes) in the incubator at 37 C, they are washed in 2 changes of distilled water and reduced in a mixture of formalin and sodium carbonate (40 per cent formalin 1 cc., 1 per cent sodium carbonate 3 cc., distilled water to make up 100 cc.). Two minutes or more will be sufficient. The yellow and gray sections are then washed in tap water and toned for 2 or more minutes in 1: 500 gold chloride, aqueous. They are passed through tap water into 5 per cent aqueous sodium thiosulphate for 2 or more minutes and then washed in water and mounted in balsam in the usual manner. Mount sections on slides from water and treat with the alcohols, flood with thin celloidin, wash in absolute alcohol, oil of Origanum (to clear) and xylol. This avoids wrinkling and tearing, and is the usual Mallory and Wright technique for mounting frozen sections. After covering the sections with celloidin, a counterstain of Van Gieson's picric acid-acid fuchsin, or of aqueous eosin may be used if desired.

Results of Silver Impregnation: With this method a complicated network of fibrils was brought out, as shown in Fig. 5. These were of

three sorts: coarse collagen fibers, fine reticulum fibers, and fibrils that were finer, usually blacker and straighter than these. All three types were intimately intermingled. The third group seemed to branch and arborize about the cells in the tumor nests. They were more numerous in the pulmonary metastases than in the meningeal tumors, although present in both situations.

In order to ascertain if possible whether these were nerve endings or not, the following stains and impregnations were used: to rule out fibroglia, the Mallory phosphotungstic acid hematoxylin stain; to rule out elastic tissue, Verhoeff's stain, and to rule out reticulum, the Bielschowsky-Maresch silver impregnation as modified by Foot.[10, 11] This was used in its two variants: the slow one with a preliminary 48 hour impregnation with 2 per cent silver nitrate followed by impregnation with silver diammino hydroxid, and the rapid one without the preliminary treatment with silver nitrate and the substitution of silver diammino carbonate for the hydroxid. This method is essentially the same as that used in the frozen sections, but differs in being applied to paraffin sections. The pyridin treatment has no particular effect excepting to cut down the chances of precipitates.

None of these methods demonstrated the fibrils seen in the frozen sections. There were occasional fibroglia fibrils in the fibroblasts, beautiful neuroglia fibrils in the brain cortex, with phosphotungstic acid hematoxylin; Verhoeff's method demonstrated elastic tissue fibers in the alveolar walls of the lung and in the vascular walls (a modification of this stain failed to demonstrate myelinated fibrils in the masses of tumor cells, although it worked perfectly in the brain tissue) and the silver impregnation of paraffin sections brought out copious collagenous and reticular fibrils in the stroma of the tumor, but no "nerve endings."

As this apparently strengthened our assumption that we had found such fibrils in the frozen sections, a method was used that employs precisely the same solutions as the one with which we had such success, but differs from it in substituting bromuration for the pyridin bath. This method had been found excellent for neuroglia cells and fibers. The bromuration was accomplished by a modified Globus technique:[7] the sections were left in 4 per cent ammonia for 24 hours, placed in 10 per cent hydrobromic acid for 8 or more hours and transferred to Cajal's fixative (15 per cent formalin, 6 per

cent ammonium bromid) for several hours, and then impregnated by the method already given for frozen sections. The result of this was striking: the fibrils were not only completely suppressed, but the reticulum impregnation was definitely enhanced; no fibrils were found running between the cells as before, while the reticulum network that forms the stroma was brought out in its most minute detail, as shown in Fig. 6. The reticulum formed baskets about the aberrant cells, but the appearance of these and the "nerve fibers" was totally different, morphologically speaking. Furthermore, this technique demonstrated melanoblasts where they had not been evident with other methods. Their melanin granules were impregnated a deep black when "ripe," brownish in the more immature cells and, in such cases, situated about the periphery of the cell in a half-moon. This method, then, affords a specific means of identifying melanin, and demonstrating melanoblasts and immature melanoblasts in tumors.

Further to check up on the nervous character of the fibers in question, sections of quiescent nevi were made and fibers quite similar to these readily demonstrated in the cell nests. They were, however, more varicose, better differentiated and thicker than those in the malignant tumors, and they were more similar to those seen in the Wagner-Meissner corpuscle. Two points remained to be cleared up: were the pictures in our cases similar to those in melanomas arising in the skin, and were the "nerve endings" demonstrable in other types of tumor? To clear the first we made sections from a melanoma of the skin over the buttock and of metastases from another case, primary in the skin, in lymph nodes. In both cases pictures quite similar, if not identical with those in our meningeal cases, were obtained. To answer the second point, sections were made from an epidermoid carcinoma of the scalp and from a fibrosarcoma of the breast. In the former, no fibrils suggesting nervous origin were demonstrable; in the latter many fine reticulum fibrils were seen, but they were totally different in their morphology and did not stain as deeply; furthermore, they were much shorter, unbranched and curly. Sections from a pigmented wart and from a small vascular nevus of the skin failed to present any fibers like the ones in question. It is not our intention to go into the matter any more closely in this paper, the subject is being reserved for further discussion in a subsequent article, after more intensive study.

Summary

Two cases of melanoma, presumably primary in the meninges, are described: one of them showed a small primary tumor in the choroid plexus with a copious petechial metastasis throughout the meninges of the brain and cord; the other was striking because of the presence of two good sized tumors in the meninges, with metastasis to the lungs, a very unusual event in the case of cerebral tumors.

It is believed that the facts brought out in the study of these cases point very strongly to the validity of Masson's argument as to the nervous origin of melanoma; these tumors had nothing to do with the skin, so far as we could ascertain, and they showed the presence of fibrils that could only with difficulty be interpreted as representing anything else but fibrils in some way connected with peripheral nerves.

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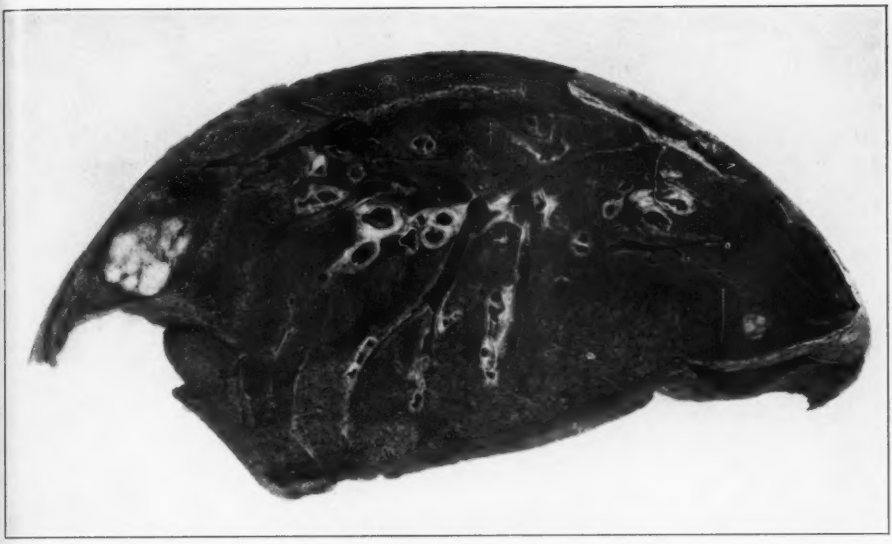
DESCRIPTION OF PLATES

NOTE. Photographs and photomicrographs taken by Mr. Joseph B. Homan of our Department of Medical Art, with the assistance of the authors. Low power photomicrographs about 200, high power about 300 diameters.

PLATE 132

FIG. 1. Photograph of a section of the lung from Case 2, showing the tumor metastases in two locations as white areas near the periphery.

FIG. 2. Photograph of two sections of the brain from Case 2, showing the large tumor with a dark, hemorrhagic core in the temporal region of the right hemisphere, and the smaller, less necrotic tumor that was situated higher and further forward in the same hemisphere.



1

2

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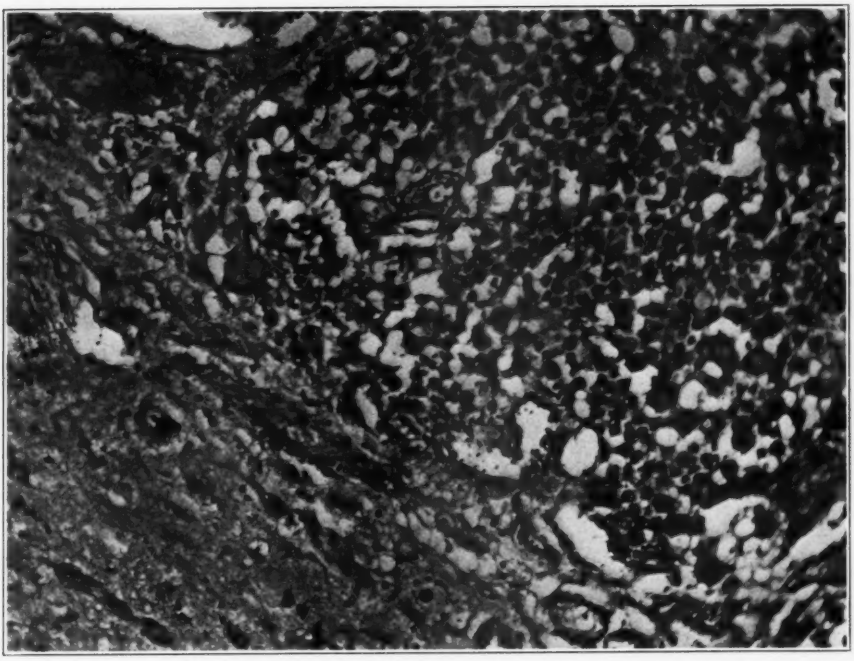
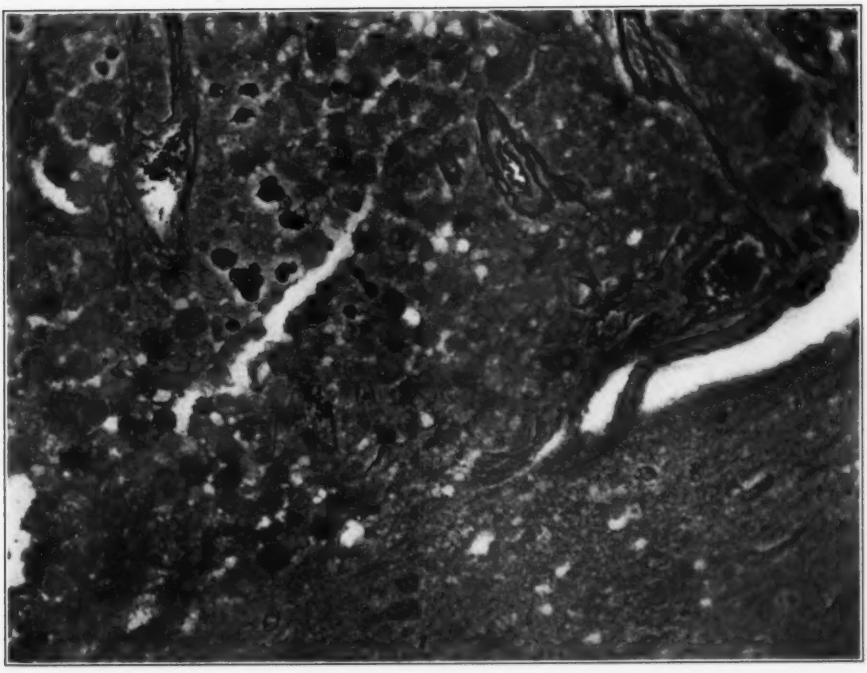
PLATE 133

FIG. 3. Low power view of silver impregnation of the smaller meningeal tumor.

FIG. 4. The same, following preliminary bromuration. Note the black-stained melanoblasts that were not demonstrable in this tumor by the ordinary, routine stains.



3



4

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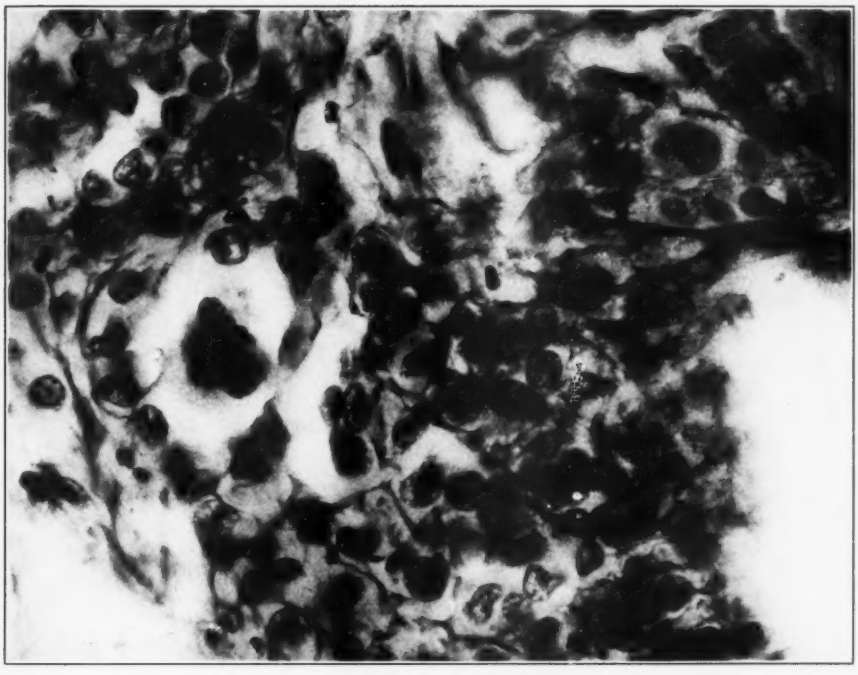
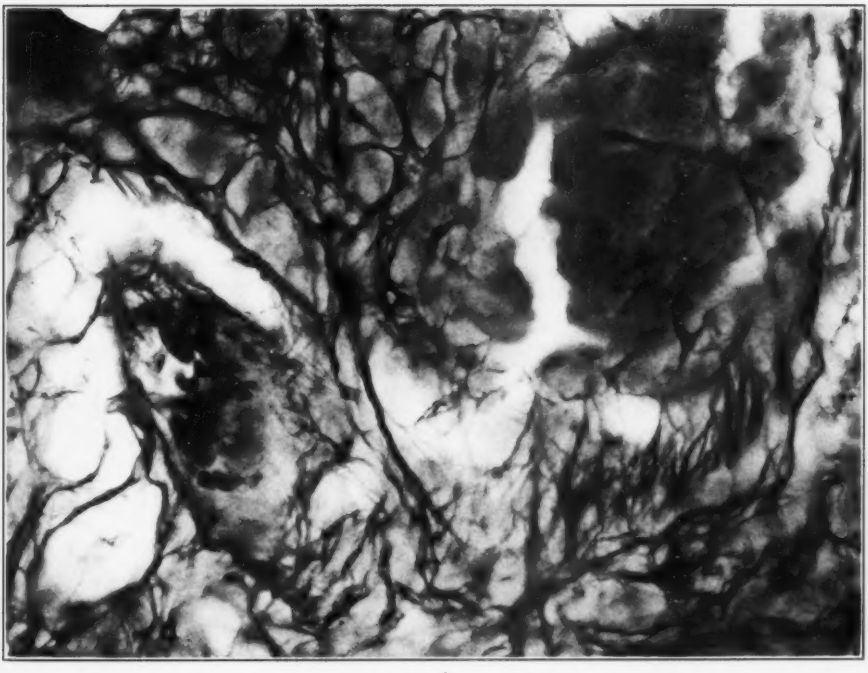
PLATE 134

FIG. 5. High power field from lung metastasis impregnated with silver. Here the varicose fibrils are well shown. Note the paler reticulum and collagen fibers in the background, also the roughly triangular shape of the varicosities.

FIG. 6. High power field, similar to the preceding, impregnated by the same method, but the impregnation preceded by bromuration, which has brought out the reticulum and suppressed the tumor fibrils and cellular detail.



5



6

Foot and Zeek Melanoma of the Meninges

ON THE SILVER IMPREGNATION OF MELANOTIC TUMORS*

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INTRODUCTION

That the pigmented nevi of the skin are, in reality, of nervous rather than of dermal origin and closely related to the neurofibromas, was the theme of an article by Soldan [1] written in 1899. He presented his theory more or less in outline and illustrated it by low power microscopic drawings that were necessarily sketchy, for which reasons one is impressed with the fact that his was a somewhat incomplete presentation of an ingenious idea, more suggestive than conclusive. The technique he employed did not permit its being more than this. Twenty-seven years later, Masson [2] published two scholarly articles on the same subject and came to essentially the same conclusions, but he followed through his line of argument much more carefully and convincingly than did his predecessor, whose work came to his notice only after he had finished his own work quite independently. According to his views, the nevi are really "neuronaevi, nervous tumors" and represent the lawless overgrowth of the cells associated with the terminal sensory nerves, as well as the proliferation of the nerves themselves. As the type cell he takes the "Merkel-Ranvier," or "naevus" cell, which may occur singly in the epidermis, clustered in small groups just beneath it, or arranged so as to constitute specialized tactile organs (Meissner corpuscles). Furthermore, he points out that in the case of nevi these cells are distributed along the trunks and branches of the peripheral sensory nerves which serve as a scaffold for the tumor, lying at first in columnar groups about the fascicles, then in nevus nests that resemble distorted Meissner corpuscles; and finally in small aggregations, or scattered singly, these cells constitute a definite adnexa to the peripheral nerve tree. Masson considers the melanoblasts, or Langerhans cells, to be specialized members of the same cell race, cells specializing in the formation of pigment, rather than serving the purposes of their more numerous, non-pigmented congeners. So well presented and

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plausible is this theory that Ewing [3] has espoused it in his textbook on neoplastic diseases, and in other writings.[4] All that remains to be done, apparently, is to improve on the silver impregnations that Masson employed and which he considered rather unsatisfactory. He frankly leaves the use of that technique to others, more skilled in the art of silver impregnation. While making no claim to be qualified for this task, it has occurred to me to employ a method that seemed promising and which has served well in demonstrating nerve fibers in frozen sections of brain. The earlier results of its use are set forth in another paper (Foot and Zeek [5]) in which it is shown to be of distinct value in connection with the demonstration of nerve fibrils in two melanomas of the meninges. It is not the purpose of this paper to expound all the theories concerning the origin of pigmented tumors; the intention is to describe the results obtained in an investigation of these by means of two modifications of a simple silver technique, focussing attention upon the theory of their nervous origin. Other histogenetic theories will thus be rejected by inference.

Technique

Fixation: The tumor tissue should be fixed for several days in 10 per cent neutral formalin, cut to 15 microns or more on the freezing microtome and the sections kept for another day in 10 per cent neutral formalin to ensure perfect fixation.

Impregnating Fluid: The impregnation depends upon the classical Bielschowsky procedure, modified so as to render the solutions that are used equimolar. The advantages of this modification have been fully discussed in a previous paper (Foot [6]) in which the findings of Kubie and Davidson [7] in this connection were tested out. The impregnating fluid is made as follows: 5 cc. of a 10.2 per cent aqueous silver nitrate solution are poured into a graduate, strong ammonia is added drop by drop until the resulting precipitate is just dissolved, and 5 cc. of 3.1 per cent aqueous sodium hydroxid solution is then added. The precipitate re-forms and must once more be just dissolved in a few drops of strong ammonia, but no more should be added after the solution clears. In this way about 12 cc. of silver diammino hydroxid is produced. It is then diluted to 50 cc. with distilled water that has been heated to about 50 C. It need not be exactly that temperature; the bath should be somewhat hotter than 37 C when the sections are placed in it.

Pretreatment of Sections:

(*a*) *Pyridin Method:* If one desires to impregnate terminal nerve fibrils and end organs, it is well to put the sections into a mixture of equal parts of pyridin and absolute alcohol for 15 to 30 minutes; they are then removed with a glass needle, touched to filter paper to remove excess fluid and transferred to a mixture of pyridin 75 parts, and glycerol 25 parts, where they remain overnight. The function of this bath is to prevent precipitates, to restrain the density of the general impregnation and thus to render more precise that of the nerve fibrils. The addition of glycerol has been found empirically to favor a more colorful metachromatic impregnation. Although the bath is not essential, its use is to be highly recommended.

(*b*) *Bromuration:* A modification of the Globus bromuration of formalin-fixed tissue may be employed to suppress the impregnation of the nervous elements, to accentuate that of the reticulum and to bring out neuroglial tissue when it is present, as in the case of brain tumors. Frozen sections are removed from formalin, soaked in 4 per cent ammonia for 24 hours (after washing off the fixative), and then transferred directly to 10 per cent hydrobromic acid where they remain overnight in an incubator at 37 C. They are then transferred to Cajal's fixative, where it is imperative that they should remain for at least 8 hours. This is composed of 40 per cent neutral formalin 15 cc., ammonium bromid 6 gm., and water to make 100 cc.

Impregnating: This is the same in the case of either pretreatment: the sections are washed in two changes of tap water and brought into distilled water, then placed in the impregnating fluid for one hour at 37 C in a tightly stoppered vessel. If the vessel be open to the air, troublesome precipitates of metallic silver will result. In this bath the sections turn dark brown, lighter if they have been bromurated.

Reduction: Sections are then well washed in two changes of distilled water and placed in a developer made up as follows: 40 per cent neutral formalin 1 cc., 1 per cent aqueous sodium carbonate (made up with distilled water) 3 cc., and distilled water to make 100 cc. This gives us a 1 per cent formalin reducer that will ensure the maximum contrast and a buffer of 0.0003 per cent sodium carbonate that will afford the most complete reduction of the silver, probably owing to its preventing the formation of formic acid. The use of a stronger buffer is to be discouraged, as it prevents the black-

ening of the nerve fibrils, making them brown instead. Two minutes or so is sufficient to develop the sections completely.

Toning: After a wash in tap water, the sections are toned for 2 minutes in a 1:500 aqueous gold chlorid solution which may be used repeatedly until grayish, monotone sections warn one that it is becoming exhausted. Merck's acid brown gold chlorid in 1 per cent aqueous stock solution has been our standard. The sections turn from brown, yellow and black to very deep violet in the toning bath.

Fixing: Sections are washed in tap water and fixed for 2 or more minutes in 5 per cent aqueous sodium thiosulphate, where they become pliable and take on a lighter, more varied color.

Mounting: It has been found best to mount the sections out of a large porcelain evaporating dish of water on clean slides, blot them dry with several thicknesses of filter paper and proceed as in the Mallory and Wright celloidin technique. Flood the slide with 95 per cent alcohol from a dropping-bottle, follow this with absolute alcohol, blot, pour on a few drops of very thin celloidin dissolved in ether and a little absolute alcohol, flood once more with absolute alcohol and blot dry with filter paper. The celloidin is cleared by flooding the slide with oil of Origanum and washing in two changes of xylol, after which a drop of Canada balsam and a coverslip complete the process. The celloidin ensures flat mounts and keeps the sections on the slides if counterstains of 5 per cent aqueous eosin, or Van Gieson's stain are desired and employed.

Remarks: Fixation should be thorough, as indicated, otherwise grayish, monotone effects will be produced. Glass needles are essential to prevent metal from coming in contact with the silver solution and when rather stout and rounded at the tip, they also prevent tearing of the sections.

Results

Pyridin Method: The keratinized epithelium is very dense and dark brown, the prickle cells of the epidermis and the cells of the mucosa slate blue, the basal cells brown, and the melanoblasts dark brown to black. The nuclei of most of the cells are brown. Collagen fibers are reddish, violet-red, to pink. Reticulum is somewhat darker, brownish to black. Neuroglia cells and fibers are grayish, rather poorly shown. Nerve fibers and terminal fibrils impregnate

dark brown to black. Muscle fibers are gray to brown, their sarcolemma black.

Bromuration Method: Keratinized epithelium brown, prickle cell layer and mucosa pale gray and stippled, basal layer slightly darker gray, melanoblasts prominent and black. The nuclei are poorly, if at all, impregnated. Collagen fibers and nerves are pinkish to violet. Reticulum is sharply black. Neuroglia cells and fibers are blackish, or dark brown. Muscle fibers are grayish, sarcolemma sharply black.

It will be seen from this that the two methods are roughly complementary; in the one the nerves are brought out, in the other the reticulum and neuroglia. It cannot be said that either method completely suppresses elements noted in the other. As they are present in both cases they will be visible, but they will tend to stand out or to retire from prominence in one or the other instance, and therefore be more readily recognized. The important thing is that the pyridin method brings out the terminal nerve fibers and their end organs, while the bromuration method suppresses these to a minimum of visibility and emphasizes the connective tissue elements at their expense, or the neuroglial, if brain tissue be in question.

Control Observations on Normal Tissue

Skin from the ball of the great toe and mucosa from the side and tip of the tongue were examined by both methods. The pyridin procedure demonstrated Meissner corpuscles, end bulbs in the subepithelial tissue and non-medullated nerve fascicles. The medullated nerve trunks were also readily recognizable. Examples of these are shown in Figs. 1, 2 and 3. One should distinguish carefully between the arrangement of nerve fibrils in the three types of structure: in the Meissner corpuscles they run in a fine network with transverse filaments connecting the peripheral, encircling ones and coursing between the transversely arranged tactile cells; in the end bulbs the fibrils are coarser and often zig-zag back and forth with triangular varicosities at the angle of their reflexion and their tactile cells are less prominent; in the fascicles the naked nerve fibers run parallel for a short distance after emerging from their myelin sheaths in the nerve trunks, to become a confused skein or tangle surrounded by a connective tissue envelope. In any case, reticulum is intimately intermingled with the nervous elements, but is not prominent unless

the sections have been bromurated. As further indication that nerve filaments are impregnated in the pyridin method one finds the terminal organs on the muscle fibers of the tongue, as well as other delicate nerve endings elsewhere.

That all of these are, indeed, nerve, or nerve sheath filaments and not simply connective tissue elements is also indicated by the fact that they are either undemonstrable in bromurated sections, or merely visible as faint shadows. Exceptions are the delicate fringe-like fibrils that border and run into the basal cells of the mucosa and epidermis, and the muscle sheaths, both of which impregnate deeply in the case of either method. The fringe fibrils stop abruptly at the basal layer in the case of bromurated sections, while they continue on into and among the basal cells in that of pyridin-silver specimens. One must bear in mind the very intimate relationship of nerve fibers and the reticulum that supports them, so that it is not strange to find them intermingled in the same structures. The Meissner corpuscles, for instance, show a reticular envelope and transverse trabeculae in bromurated sections, but the nerve filaments and the tactile cells are reduced to mere shadows, so that one seems to be looking at an empty hull.

Pigmented Nevi

A number of nevi of various sorts were collected from the dermatological clinic and the autopsy table and examined by means of the above methods. It is interesting to find how extremely easy it is to collect moles at autopsy, as well as to observe how varied is their nature. The term "nevus" is admittedly very loose and several tumors or congenital defects are classified under this name. We are not interested in the vascular nevi, or the pigmented warts (Fig. 4), or papillomas, in this paper, excepting as they show a complete absence of "nevus nests" and the filaments that characterize these.

The pigmented, melanotic or neuronevi may be divided into two main subclasses, the superficial and the deep, as Masson has indicated. Various subheadings of these two divisions could readily be devised according to the presence or absence of pigment, the papillary or non-papillary character of the epidermis, and so on. The situation of the tumor, whether deep or superficial, seems to determine real differences in its architecture and may therefore be

useful in classification. Even so, any attempt at strict subclassification appears to be rather futile on account of the essentially close relationship of the various tumor elements to each other.

Superficial Neuronevi: A study of these showed Masson's description to be exceedingly accurate. All that remains to be added to it is the fact that the distribution of nerve filaments among the nevus cells is even more elaborate and copious than he has indicated. It was found that large nerve trunks entered the base of the tumors, branched and in turn gave off the non-medullated fascicles stressed by Masson. These then appeared to break up into broad, reteform sheets that became subdivided into naked fibers that branched and finally terminated in very delicate fibrillae that arborized about the cells of the nevus nests. The nests were found to be distributed as Masson has so well described: at first elongated and columnar about nerve fascicles, later spheroidal and more closely resembling distorted Meissner corpuscles. In fact, one could pick out isolated instances where the resemblance was so striking as to give rise to doubt as to whether one were not observing a normal corpuscle rather than a nevus nest. The nests extended up into the dermal papillae and were not infrequently covered by a comparatively thin layer of epidermis. There was never any question as to distinguishing between epidermal and nevus cells — with the silver impregnation their appearance is totally dissimilar. The epidermal cells were quite free from fibrils, rather granular, decidedly denser than the nevus cells which were pale, possessed of vesicular nuclei and usually surrounded by the arborizing nerve endings, as seen in Figs. 5 and 6.

Most of the moles collected showed slight variations of this picture. In some there was scarcely any melanin, excepting for a variable amount in the basal layer of the epidermis; in others this was very considerable and there was "spilling over" into the melanoblasts of the nevus nests near the epidermis. The nerve filaments, too, varied from extremely delicate tendrils to rather stout fibrils; one tumor would show one variety (particularly a pedunculate "white mole"), while another would show coarser fibrils with less tendency to elaborate arborization among the nevus cells. There was also marked variation in the amount of collagen and reticulum in the specimens collected, but most of them showed an almost fibromatous proliferation of collagen fibers about the nerve trunks and fascicles near the base of the tumor. One or two tumors showed

a tendency on the part of the nevus cells to differentiate into melanoblasts, or Langerhans cells (Fig. 7), in which case the innervation of the nevus nests was much less complex and striking than in the more usual variety. The fibrils tended to be much coarser in the melanoblastic type. The factor of pigmented nevus cells has strikingly little effect upon the gross appearance of the mole, for some very brown moles were found to have the pigment concentrated in the basal layer of the epidermis, while the melanoblasts in the nevus nests were very few in number. An equally brown mole might show the reverse picture microscopically, with numerous melanoblasts in the nevus nests and no particular increase in the epidermal pigment.

Deep Neuronevi: These showed the nevus nests to be more deeply situated in the derma and to have an affinity for the deep hair follicles, alongside of which they were apt to be concentrated (Fig. 8). The nests showed a closer resemblance to end bulbs, or to the tangled nerve fascicles than they did to Meissner corpuscles. This is natural when one takes into consideration their situation, which is closer to those structures than to the more terminally situated tactile bodies (Fig. 9). In this case, too, there was marked proliferation of connective tissue elements about the nerve fibers and nevus nests and the similarity to neurofibroma was even more striking. Unfortunately, this type of tumor was in the great minority of those collected, so that it could not be studied as intensively.

In all cases, bromuration brought out the connective tissue elements at the expense of the nervous, just as in the controls on normal tissue, and indicated that the latter were nerve and not reticulum fibrils.

Malignant Neuronevus — Melanoblastoma

Logically following the classification, we come to the malignant members of the group, the melanoblastomas, so-called "melanosarcoma" and "melanocarcinoma." It seems futile to attempt a rigorous classification of these, since they are completely lawless and defy classification. A number of examples were collected; malignant melanoma of the skin, two cases originating in the meninges, a metastasis from a dermal melanoblastoma to the axillary nodes, and so on. They all conformed to one loose law, however, in that they resembled the benign forms in their general arrangement and in the fact that they invariably possessed the elaborate neurofibrils of

these, possibly less well organized and differentiated. It was also noted that some of them tended to produce the amelanotic cell nests, while others ran to the production of melanoblasts at the expense of nevus cells. They tended to be superficial and to extend well up into the epidermis, but as they showed progressively invasive growth at the base, they also extended more or less deeply into the derma. Some of them exhibited marked connective tissue proliferation; others were of a more adenoid type and tended to ape adenocarcinoma in their arrangement and appearance, particularly in their metastases. The structure of these tumors is too well known to warrant further description here — suffice it to say that their relationship to the benign pigmented nevi, or neuronevi, was strikingly manifest in most instances. Only when they became so anaplastic as to resemble adenocarcinoma did their resemblance lag, and in these cases one could still always find some areas where it was still maintained, particularly between the cell nests where younger aggregations of cells still held to the nevic type of growth. A melanoblastoma is shown in Fig. 10.

Discussion

In the earlier paper [5] it was shown that the fibers of these tumors were not demonstrable by the methods devised for specifically staining collagen, reticulum, fibroglia, elastic tissue, neuroglia and the like; it was also noted that no such fibrils, presumably of nervous origin, were present in the cell nests of epidermoid carcinoma (which would probably resemble melanoblastoma the most closely) or in fibrosarcoma (which possesses innumerable reticulum fibrils), see Figs. 11 and 12. The bromuration method, as I have repeatedly stressed, strengthens one's belief in this nervous origin.

Masson has covered the theory of the histogenesis of this tumor group very thoroughly, so that it would be presumptive to repeat what he has already said, but one might elaborate on his ideas a little. For example, it is not to be understood that the Meissner corpuscle is necessarily the starting point for the tumor; some nevus nests resemble this organ very strikingly and, in such cases, it may well have been their point of origin; others, however, more nearly resemble end bulbs, still others nerve fascicles and some may show so much fiber proliferation that the nevus cells become obscured.

Some of them, as has been remarked, show a tendency toward the production of melanoblasts. It therefore seems obvious that any, or all of the cells of the sensory nervous adnexa might be considered as type cells of the same cell race ("*de la même souche cellulaire*," as Masson puts it); even the sheath cells of Schwann, which have long been considered by embryologists as neuroglial, in contradistinction to the mesoblastic cells of the adnexa, must be considered as potential participants in the process. The variegated appearance of the malignant types of the tumor would strengthen the assumption of racial similarity between the cells of the adnexa. One might, then, speak of "neurofibroma" developing up to the point where the myelin sheath ends in the nerve trunks and of "neuronevus" when the tumor is situated beyond that point, including the end organs of the nerve.

Criticism of this theory may be foreseen and, one hopes, partly forestalled. A criticism directed toward the question of the nervous character of the end fibrils under discussion has been answered to the best of my ability in this paper. Another criticism, already encountered in personal discussion, centers about the point as to the production of these fibrils — do the tumor cells produce them? Obviously not, for nerve fibers are the prolongations of the axones of nerve cells and as these fibrils are found in the benign and malignant nevi, and in the metastases of the latter as well, they must be accounted for. This can best be done on the basis of "innervation." Is it not probable that the proliferation of the cells of the adnexa provoke a proliferation of the nerve, or nerve sheath fibrils from their parent stalk, as it were? Do not nerves grow out in just this manner into the various embryonal primordia and in regenerating nerve stumps, and could this not be a similar process of growth?

Another criticism might rest upon the absence of such tumors, as a rule, from sites liberally supplied with Meissner corpuscles — the tongue, the balls of the fingers and toes and the like. This criticism is of merely negative value and lays too much stress on the nervous elements. If Meissner corpuscles, or nerves for that matter, be present in a certain area, such tumors could well arise there, but they need not necessarily do so.

Summary and Conclusions

The microscopic examination of material from normal skin and mucosa, a variety of nevi and several melanoblastomas, by means of a thoroughly reliable silver impregnation, seems to bear out Masson's theory as to the nervous character of pigmented moles and their malignant relatives. That the "Merkel-Ranvier," or "nevus" cell, divisible into tactile cells of various sorts, and the cells of the non-medullated nerve fascicles, all represent various phases in the life of one cell type in these tumors seems fairly evident, if not proved. That these cells may take the form of scattered individuals, nests resembling Meissner corpuscles, melanoblasts, or neurofibromatoid complexes seems clear. In the case of the malignant tumors, it is only natural to expect more or less atypical growth and anaplasia and a return to structures representing stages in the fetal development of the cell. Alveolar and gland-like structures seen in "melanocarcinomas" should not, therefore, prove to be a very disturbing note in the theory.

The silver impregnation as a means of recognizing and classifying these tumors cannot be too highly recommended; it is simple in operation and actual experiment proves that it can be successfully carried out at the very first attempt. It is to be regretted that it cannot, as yet, be successfully applied to paraffin sections, but as experiments are now under way, this difficulty may be solved. The striking difference between the epidermal and the nevus cells, when impregnated by this method, is at once evident, the association of fibrils with the latter affording a reliable criterion that is immediately applicable. In closing, it would not be trite to reiterate Masson's warning to investigators along these lines; please do not rely upon old and outworn methods while endeavoring to check up on this theory, but use those that Masson has perfected, or the one herein described.

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DESCRIPTION OF PLATES

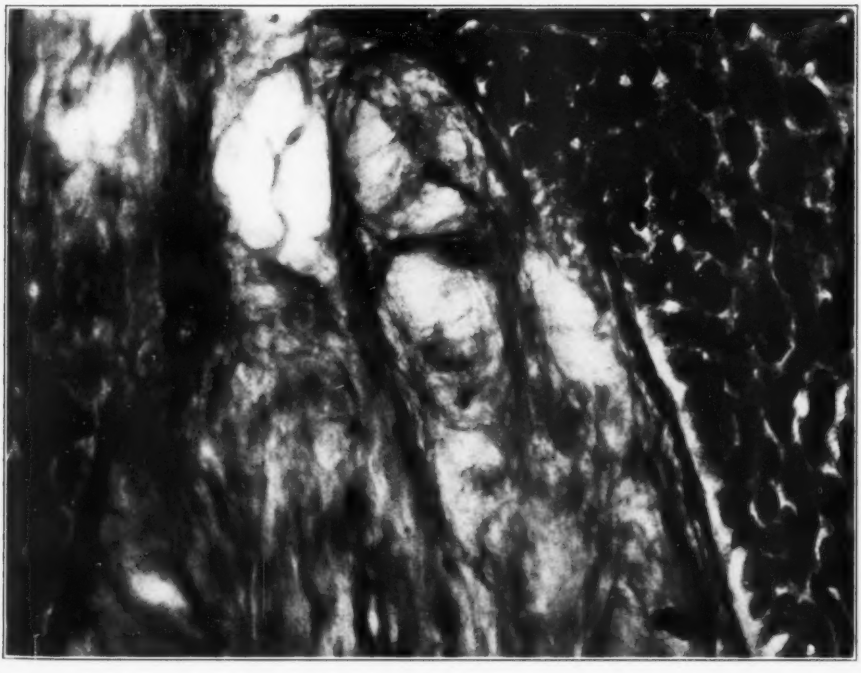
NOTE. All the photomicrographs were taken by Mr. Joseph B. Homan of our Department of Medical Art, assisted by the author. They were made from frozen sections impregnated by the pyridin-silver diammino hydroxid method described in this paper. The low power pictures show about 200, the high power about 800 diameters enlargement. No counterstain was used in any instance. The detail in the photographs, particularly Fig. 10, shows the excellence of the method for general purposes of photomicrography, such as the bringing out of nuclear detail, and the like.

PLATE 135

FIG. 1. Low power view of a group of Meissner corpuscles in the submucosa of the tip of the normal human tongue. They project upward between the epithelial papillae.

FIG. 2. High power detail of the tip of one of the above corpuscles, from the same field. Note the complexity of the arrangement of the fibrils and their transverse distribution.

1



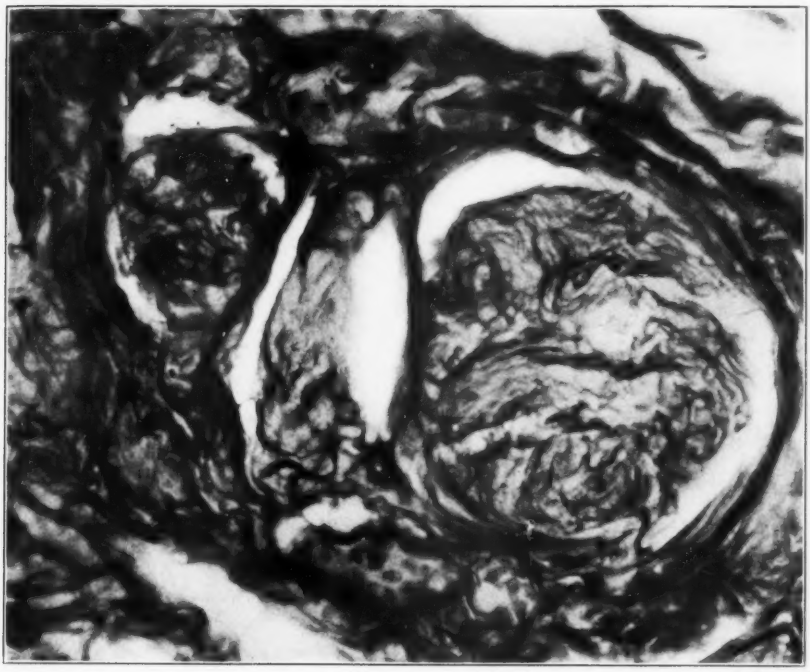
2

Foot Silver Impregnation of Melanotic Tumors

PLATE 136

FIG. 3. High power view of a group composed of a nerve fascicle containing medullated and non-medullated fibers, and of an "end bulb," smaller than the fascicle, with a vessel lying between them. Note the fibers entering the bulb at one side. These structures often lie near the smaller vessels of the tongue.

FIG. 4. Low power picture of a pigmented wart, or papilloma. Note that the pigment, impregnated black with silver, is limited to the cells of the basal, epidermal layer. There are no nevus nests to be seen.



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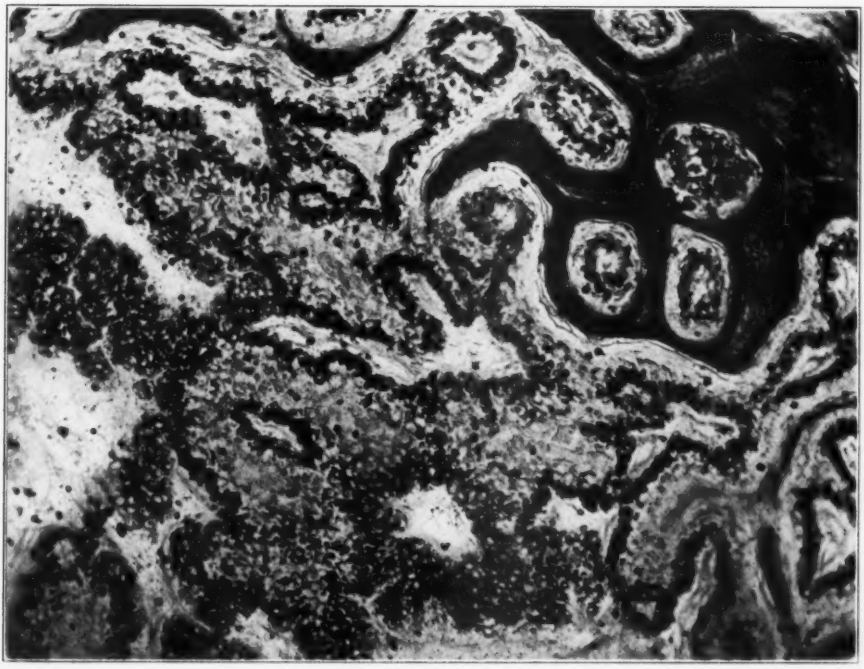

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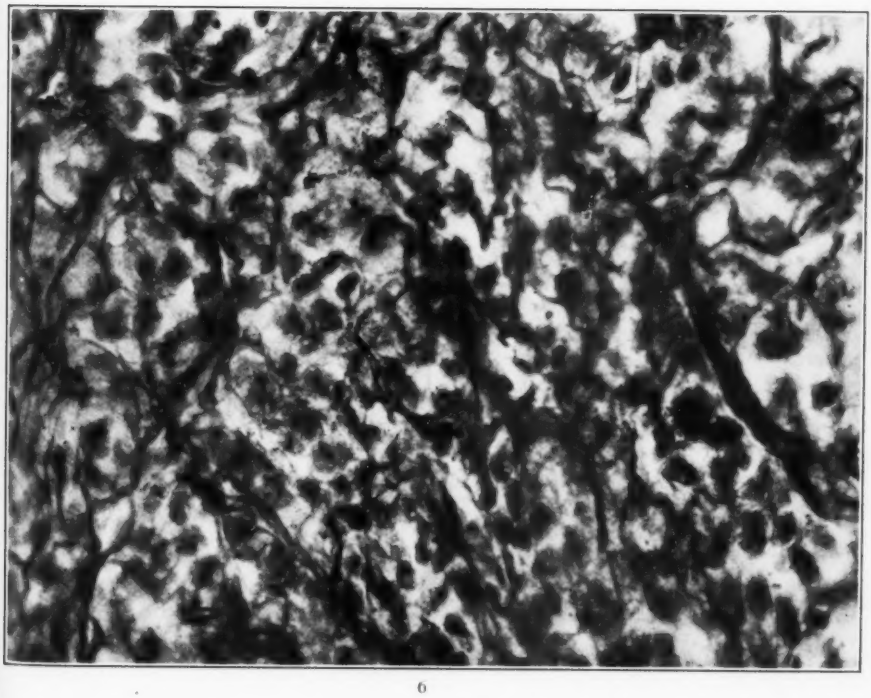
Foot Silver Impregnation of Melanotic Tumors

PLATE 137

FIG. 5. Low power field of a non-pigmented mole or "white nevus," to show the nevus nests lying superficially and extending out nearly to the surface. Note the marked difference in the appearance of the nevus, the epidermal cells and the fringe fibers that normally run between derma and epidermis, running between the nevus cells and the epidermis in this case.

FIG. 6. High power view of a superficial, pigmented, non-papillary nevus, to show the complex fibrils that branch and arborize amongst the cells of the nevus nests. Here and there varicosities may be seen on the coarser fibers.

5



6

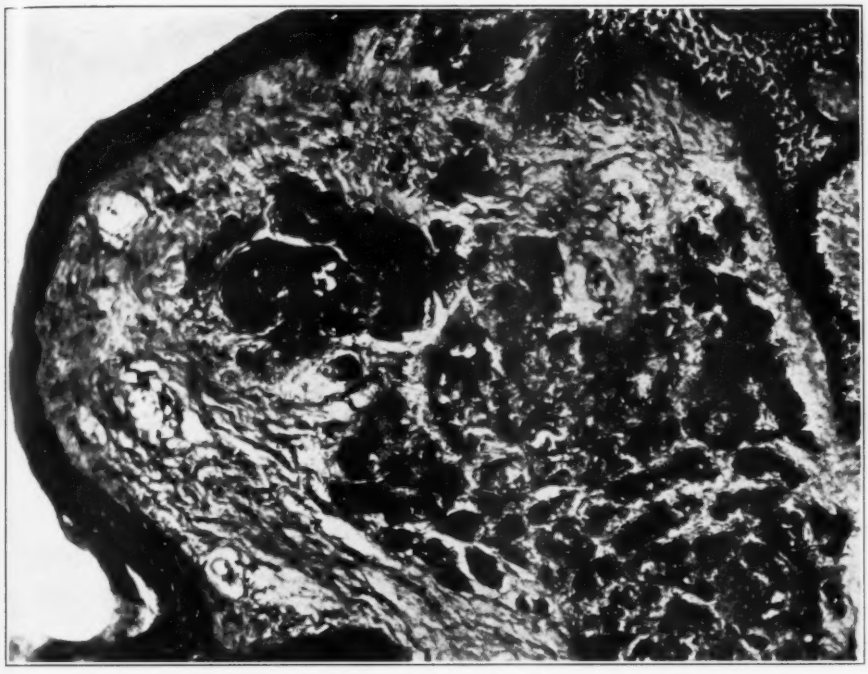
Foot

Silver Impregnation of Melanotic Tumors

PLATE 138

FIG. 7. Low power view of a superficial "melanoblastic" nevus. Note the nests of melanoblasts deeply impregnated with silver and the comparative scarcity of fibrils in these. Other nests in the same tumor were comparable with those in Fig. 6, although their fibrils were much coarser and their cells more sparsely strewn.

FIG. 8. Low power topographic view of a deep nevus, showing the comparatively unaffected epidermis and "pars papillaris" of the dermis, the tumor lying almost in the subcutaneous tissue. The pigment in this "brown spot" is concentrated in the basal layer of the epidermis. Note the nerve trunk entering the area of nevus nests and branching to form a reteform plexus in which their cells are embedded.



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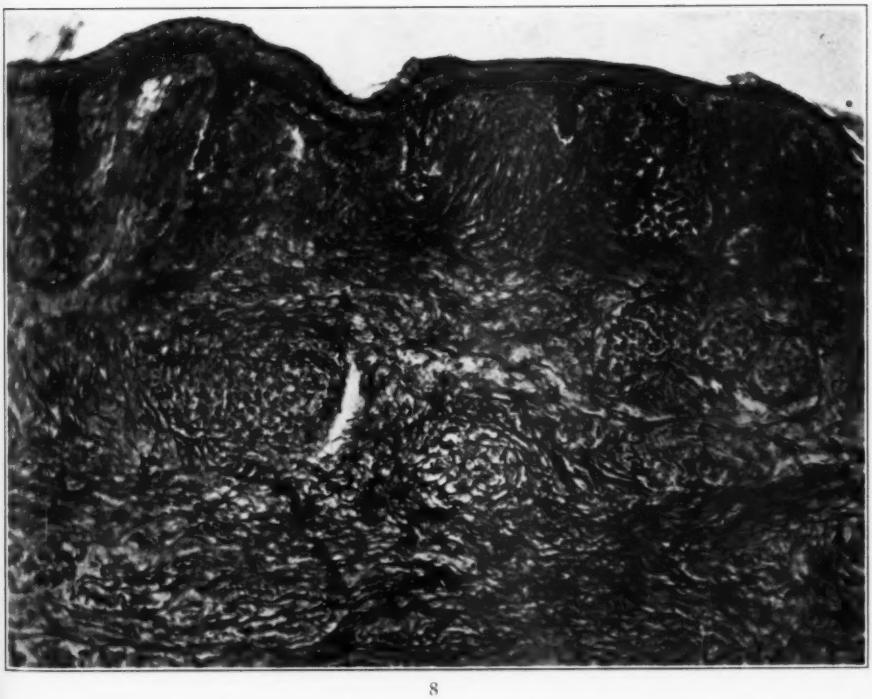


8

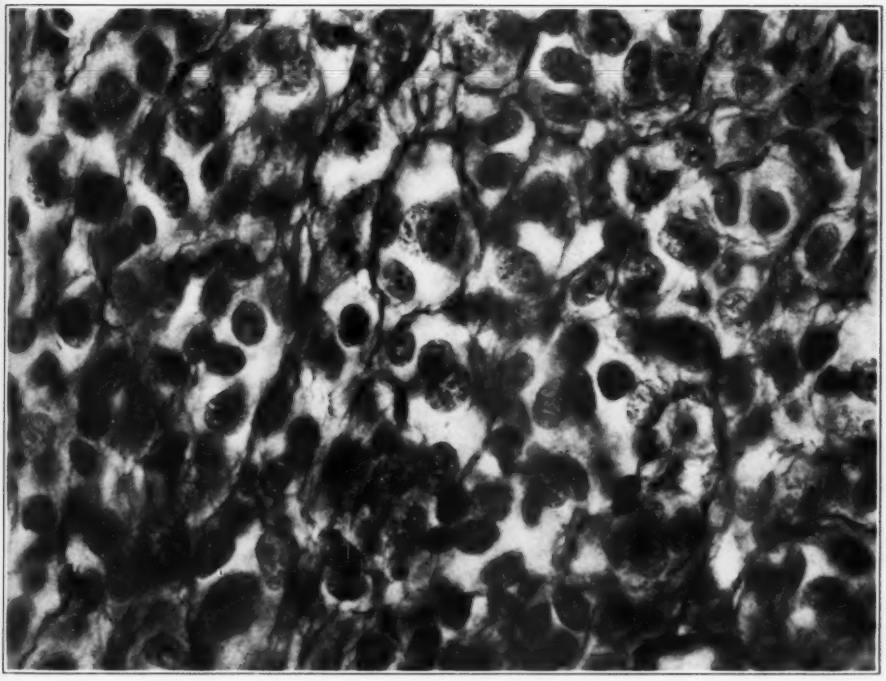
Foot Silver Impregnation of Melanotic Tumors

PLATE 139

FIG. 9. High power detail of a nerve in which are embedded a number of nevus nests, taken from the tumor shown in Fig. 8. The black masses of material are silver precipitate, the result of impregnation in an open vessel. The specimen was impregnated during the experimental stage of the investigation and had to be used for illustration as no other deep nevus was collected after the method was perfected.

FIG. 10. High power field from a melanoblastoma of the buttock ("malignant melanoma"), showing very delicate fibrils in all their ramifications.

9



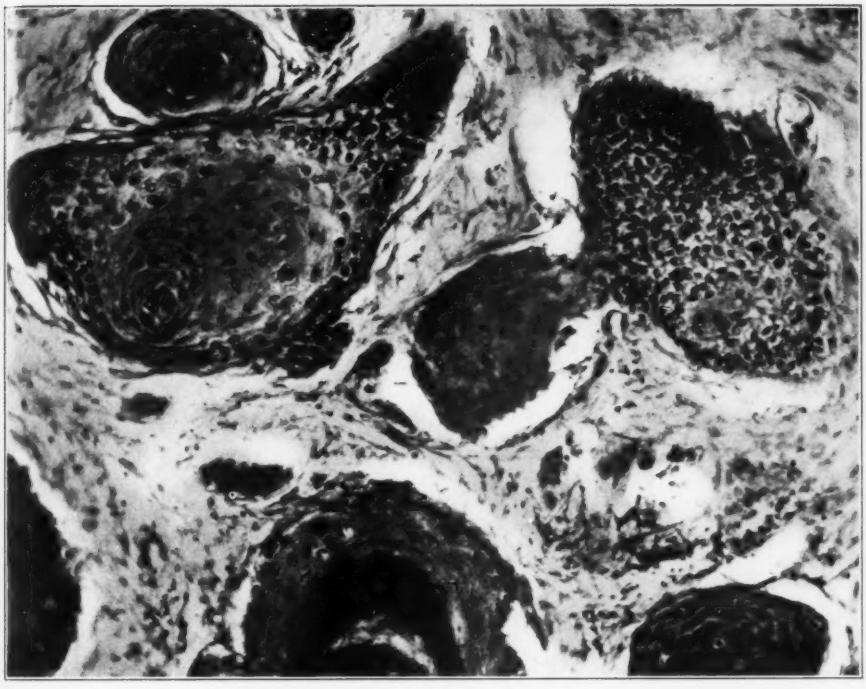
10

Foot Silver Impregnation of Melanotic Tumors

PLATE 140

FIG. 11. Low power view of an epidermoid carcinoma to show the absence of fibrils from the tumor cell nests.

FIG. 12. High power field from a fibrosarcoma of the breast showing the dissimilarity of the fibrils of such a tumor to those of the nevus group. These are reticulum fibrils, for the most part, and do not branch, neither do they terminate in arborizations around the tumor cells as do those of the nevic tumors.



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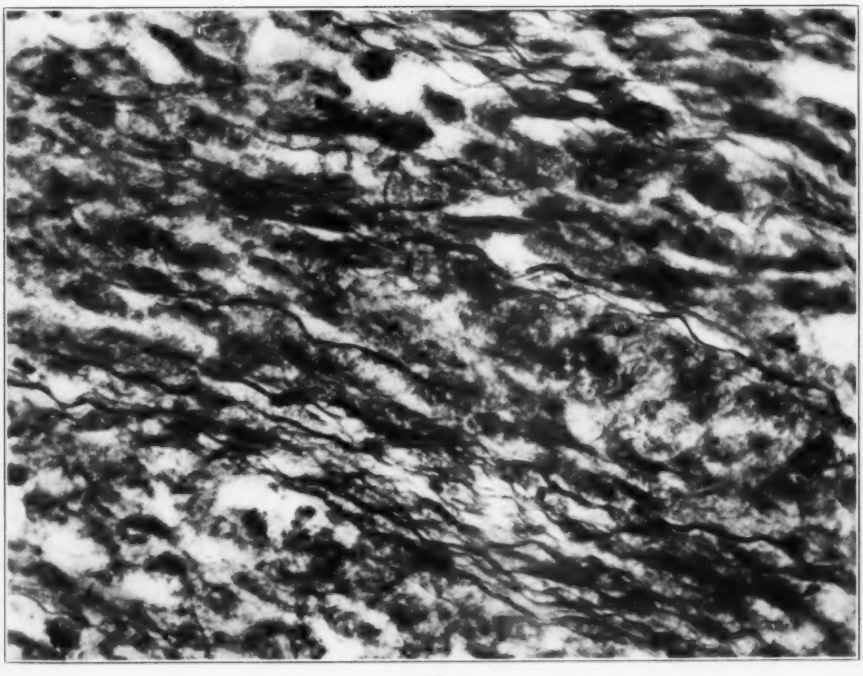

12

Foot Silver Impregnation of Melanotic Tumors

MASSIVE UNATTACHED RETROPERITONEAL TUMORS *

AN EXPLANATION OF UNATTACHED RETROPERITONEAL TUMORS BASED ON REMNANTS OF THE EMBRYONIC UROGENITAL APPARATUS

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The occurrence of retroperitoneal neoplasms arising independently of the adult urogenital organs has, to date, eluded scientific explanation. Until about 1880 these tumors were diagnosed as sarcoma or pancreatic cyst, and dismissed without further consideration or study. Howship in 1871 had observed a composite tumor possessing certain characteristics similar to dermoid teratomas commonly found in the ovary. In 1889 Bassini described a cystic adenoma morphologically resembling a pseudomucinous cystadenoma of the ovary, and Frank in 1894 observing a similar tumor attributed its histogenesis to an accessory ovary. Since 1894 instances of unattached retroperitoneal tumors have been reported in the medical literature averaging somewhat less than one case a year. Occasionally, authors of these case reports have added to the diversity of histological features that may be associated with these neoplasms. These now include glomeruli, renal tubules, rete structures, bone, hair, sweat glands, fat, smooth muscle, uterine mucosa, chorion epithelium and so on.

We have been privileged to study seventeen cases of unattached retroperitoneal tumors, and having correlated our findings with the available information obtained from the literature we believe that there is a general explanation for the genesis of these tumors, namely, that they arise from remnants of the embryonal urogenital apparatus. This concept would account for the histological structure, as well as diversity of histological elements of these tumors. It would also account for the fact that, with few exceptions, well established tumors found in the adult urogenital organs have also been found free retroperitoneally. In fact this concept would seem to unify all

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the pertinent facts known with regard to unattached retroperitoneal tumors, and this we shall endeavor to substantiate in the following review.

Review of Embryology of the Urogenital Apparatus

This is intended to be a very brief review of the embryology of the urogenital apparatus and its purpose is merely to orient the reader with regard to facts he may not readily recall.

Structures to be discussed in this résumé are:

1. Pronephros.
2. Urogenital fold.
3. Mesonephros.
4. Metanephros.
5. Genital cell.
6. Genital gland.
7. Müllerian duct.
8. Adrenal cortex.

The last is added because in development it is closely associated with the urogenital apparatus.

The following points will be considered:

1. Origin of the structure.
2. Time of appearance, time of complete development and time of degeneration (if such occurs).
3. Extent of the structure.
4. Participation of the structure in the formation of adult organs.
5. Anatomical relationships of the developing structures.

1. *Pronephros:* The pronephros forms from the primitive segment stalk (cephalic end of the nephrogenic cord) by an evagination of the celomic epithelium into the parietal mesenchyme. In the human the first anlage is in a 1.73 mm. embryo. Complete formation is almost reached in a 2.5 mm. embryo (23 pairs of segments), and degeneration is well advanced in a 4.25 mm. embryo. The approximate stage of complete disappearance is the 4.9 mm. stage. The pronephros extends from the seventh to the fourteenth primitive segments. A pronephric segment consists of a principal tubule, a nephrostome canal and a glomerulus. The segments are connected by a collecting duct (Wolffian duct). The free terminal part of the excretory duct probably forms "in loco" from the mesenchyme. It

develops in embryos between the 14 and 23 segment stages and reaches the cloaca in an embryo with 27 pairs of segments. This duct is located in the parietal mesenchyme just beneath the ectoderm. The pronephric segments completely degenerate, but the excretory duct participates in the formation of the mesonephros.

2. *Urogenital Fold:* This fold contains the mesonephros, genital gland, Wolffian duct and Müllerian duct. A fold forms because there is not sufficient room retroperitoneally for the developing structures and they invaginate into the celomic cavity. The fold is first seen in a 2.5 mm. embryo, when it extends from the fifth cervical to the eighth dorsal segment. Growth and degeneration are caudad and by the 50 mm. stage the fold extends only from the fourth to fifth lumbar segments. These urogenital folds are found on either side of the midline and undergo certain changes.

(*a*) The fold becomes divided into four parts by evaginations of the celomic cavity (a lateral tubular part, a ventral genital part, a dorsal glandular part and a medial mesentery portion). The Müllerian duct, genital gland and mesonephros develop in the first three parts respectively.

(*b*) Caudad, the two folds unite to form the urogenital cord, which divides the pelvis into an anterior and posterior part. The union of the Müllerian ducts is thus permitted. The relationship of the various structures in the fold can best be seen in Diagrammatic Drawing 1.

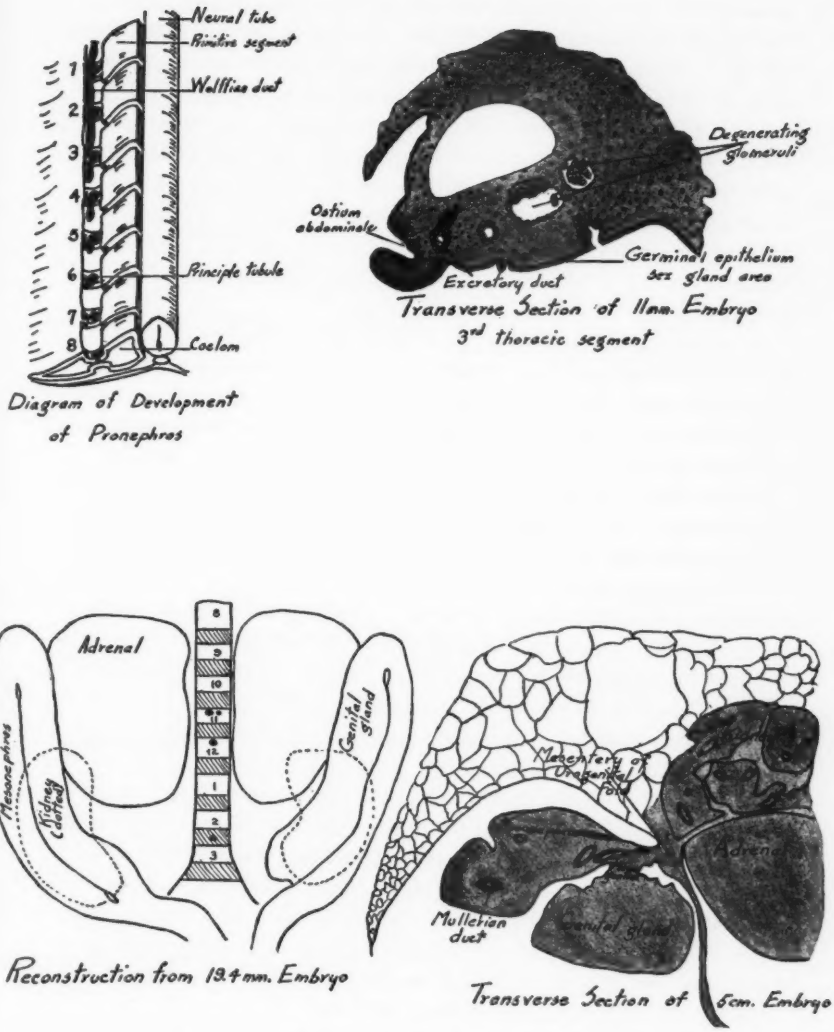
3. *Mesonephros:* The mesonephros forms from the middle and major portion of the nephrogenic cord, overlapping cranially to some extent with the pronephros and extending caudad to the twenty-sixth or twenty-seventh primitive segment. It extends over approximately 18 segments and in all about 83 tubules form. This first appears in the 2.5 mm. stage. Growth and degeneration can be followed in Text-Fig. 1. The first anlage is a vesicle which forms the principal tubule. It establishes connection with the Wolffian duct laterally. A supplemental tubule forms mesially later, making an S curve and uniting with a glomerulus. Degeneration is divided into two stages, the first of which is complete in the 21 mm. embryo. It includes the upper 57 tubules, no part of which participate in the formation of adult structures. Thus, at this stage (21 mm.), the mesonephros consists of the lower 26 tubules and extends from the second to the fourth lumbar segments. In the second period of

degeneration the glomeruli and secretory tubules degenerate, but the excretory tubules and corresponding part of the collecting duct become further modified to establish connection with the genital gland, forming the epigenitalis and the paragenitalis. For this function there must be a urogenital union which occurs between the rete of the genital gland and the excretory (transverse) tubules of the mesonephros.

4. *Metanephros:* The metanephros develops from two systems: (1) the metanephrogenic tissue which is the lower 1 to 2 segments of the nephrogenic cord, and (2) the ureter bud which appears from the Wolffian duct just proximal to the cloaca. The glomeruli and secretory tubules are from the former, and the collecting tubules, pelves and ureters are from the latter. The ureter anlage first appears in the region of the fifth lumbar segment in an embryo of 5.3 mm. greatest length. This ureter bud is capped by the metanephrogenic tissue which becomes displaced from the nephrogenic cord by dorsal growth of the ureter. After reaching a dorsal position growth is in the cephalic direction, reaching the first to second lumbar segment. The metanephros is then in the approximate location of the adult kidney. Complete development of the metanephros does not occur until after birth. There is no degeneration of this structure.

5. *Genital Cell:* The origin of the genital cell is disputed, but in general two theories of significance are offered. The first theory is formation from the celomic epithelium "in loco." Authors proposing this theory think that the celomic epithelium possesses the potency of forming reproductive cells. A second theory is the derivation of the genital cell directly from segmentation cells. Hence, it becomes necessary for the genital cells to migrate from their site of formation into that part of the celomic epithelium which is destined to become the germinal epithelium. Here, it seems, genital cells might easily stray to foreign locations.

6. *Genital Gland:* The genital gland forms from the celomic epithelium covering the ventral part of the urogenital fold. The gland is at first indifferent. The anlage is first seen in a 4.9 mm. embryo, located between the first and third dorsal segments. It appears as a thickening of the germinal epithelium which becomes multilayered. Later, the epithelium invades the mesenchyme which compresses it and pushes the mesonephros dorsally. The genital fold is then formed by evaginations of the celom, and the genital gland and



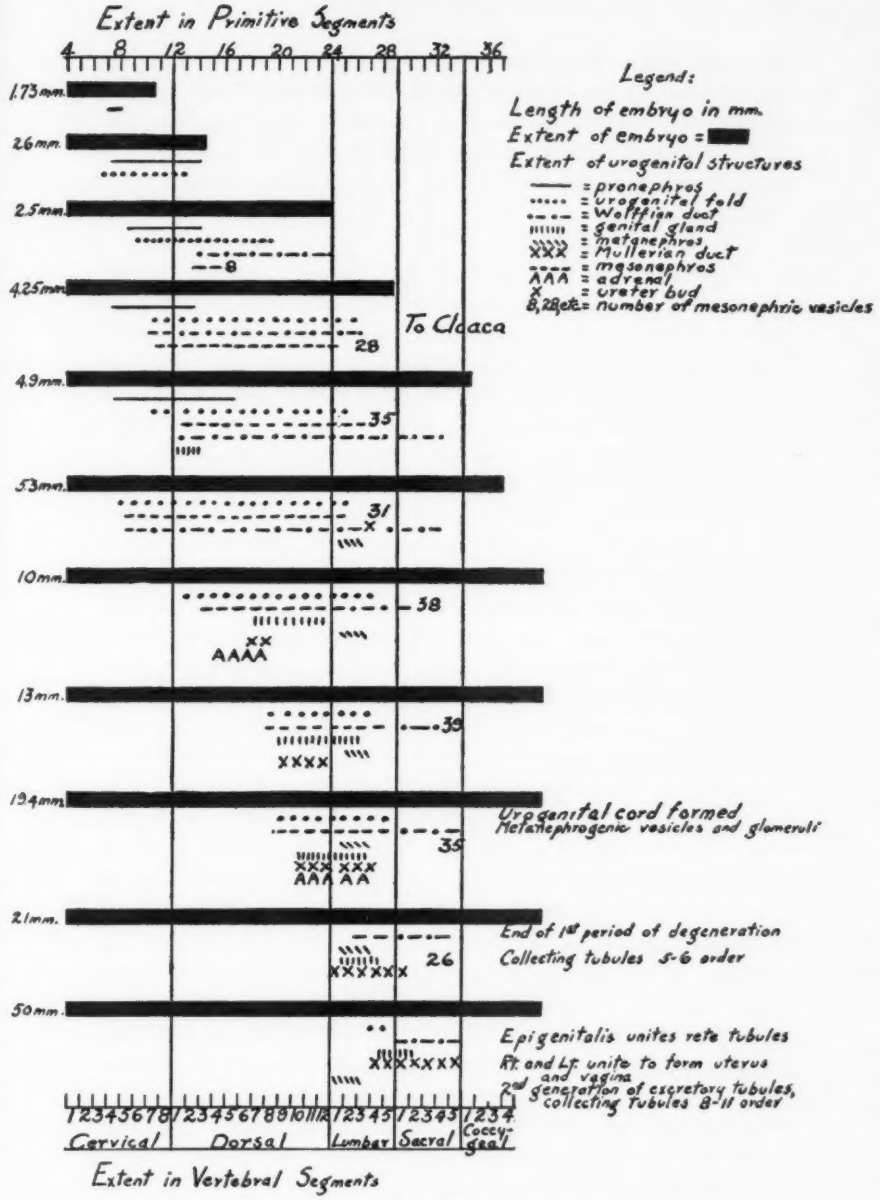
DIAGRAMMATIC DRAWING I

Relationships of urogenital organs. Compilation from Keibel and Mall

mesogenital become definite structures. The indifferent gland is a homogeneous mass of epithelial cells in intimate contact with, but definitely separated from, the collecting tubules of the mesonephros. The extent of growth and degeneration can best be followed in Text-Fig. 1. The maximum extent of this structure is 14 segments, but the upper 10 to 12 degenerate and eventually only 2 to 4 remain to form the adult organ. Differentiation into the male sex gland begins at about the 13 mm. stage, or into the female gland at a somewhat later stage. It seems unnecessary to say more than that the differentiated sex organ is formed from this epithelial mass and that urogenital union occurs as mentioned above.

7. *Müllerian Duct:* The ostium of the Müllerian duct is formed by an invagination of the celomic epithelium into the summit of the urogenital fold. The tubal portion forms from a caudal growth of this blind end. The anlage of the ostium is first seen in an embryo of 10 mm. greatest length at the level of the third dorsal segment. The blind end grows caudad in the lateral (tubal) portion of the urogenital fold to reach Müller's tubercle, located in the dorsal wall of the vesico-urethral anlage. This occurs in embryos between 21 and 27 mm. greatest length. The two ducts unite in the urogenital cord in embryos of about 28 mm. length. In the female there is no degeneration, but descent occurs as the body of the embryo grows cranially, and later rotation occurs. The entire structure remains to form the fimbria, fallopian tube, uterus and vagina. In the male, degeneration is complete except for the hydatid of Morgagni and the sinus pocularis, male vagina.

8. *Adrenal Cortex:* The adrenal cortex develops from the celomic epithelium, the first traces appearing in the 6 mm. embryo. The epithelium thickens and invades the mesoderm ventrolateral to the aorta, and mesial to the urogenital fold. With increase in size of the gland it projects into the celomic cavity, forming the suprarenal ridge. This is between the mesonephros and the mesentery. In an 8 mm. embryo the glands are already definite organs completely separated from the celomic epithelium, and vascularization occurs in the 9 mm. stage. Differentiation of the cortex into three layers takes place rather late. No degeneration occurs. Accessory nodules of cortical tissue are of frequent occurrence and may be found in the following locations: (*a*) suprarenal capsule; (*b*) broad ligament; (*c*) hilum of sex glands; (*d*) region of the spermatic vessels; (*e*) kid-



TEXT–FIG. 1

Status of urogenital apparatus in embryos from 1.73 to 50 mm. in length.

ney; (*f*) liver, etc. Theories as to the origin of these accessory nodules are: (*a*) breaking and displacement of cortex by invasion of medulla; (*b*) inclusion of cortex in adjacent developing organs; (*c*) formation of cortical tissue from transverse tubules of the mesonephros, and (*d*) inclusion of celomic epithelium which has the potency to form adrenal cortex.

Presentation of Material

Information concerning tumors of the urogenital apparatus is widely scattered in the medical literature of the world. It is to be found in articles usually comprising single case reports. Some authors have chosen to interpret the pathogenesis of their peculiar case, while others have contented themselves with the report of an unusual case. More attention has been given the subject in Germany than in all other countries combined. Only four references to this group of tumors were found in the American medical literature. In three of these four instances, according to the authors, the tumors arose from the mesonephros, while no definite interpretation was given for the small round cell tumor in the fourth report further than to assume that it was a rapidly growing portion of a mixed tumor because it arose in the kidney region. Nowhere has there been an attempt to survey the morbid anatomical conditions on the broad basis of anomalous unabsorbed residues in the development of the urogenital apparatus.

A summary of the information which has accrued can be concretely presented in tabular form. A natural division of the material is immediately apparent. Similar to tumors in the adult urogenital organs, the tumors from their remnants are both solid and cystic. The cystic and solid tumors are segregated in two tables for consideration.

The tabulation shows that cystic tumors of this group have been known since 1871, when a retroperitoneal dermoid teratoma similar to the dermoid teratoma of the ovary was described. It is natural that this type of tumor should be recognized, first because hair and well formed bone are easily identified grossly and the grumous greasy material of epithelial cysts is very characteristic. In 1889 Bassini first described a tumor which, if located in the ovary, would have been diagnosed cystadenoma of the ovary. Frank, in 1894, after giving a description of a similar tumor, stated that the lesion

was identical with cystadenoma of the ovary. The theory was then launched that these unattached cystadenomas had their origin in accessory ovaries. Goebel, in 1901, in the interpretation of the histogenesis of his case of dermoid teratoma came to the conclusion, after a lengthy discussion of teratology in which the possibility of a sex cell origin was included, that the tumor under consideration had its origin in a bigerminal inclusion. Up to the present time this interpretation has not been further clarified. On the other hand, the cystadenoma type of lesion has apparently been put upon a firm foundation. Subsequent to Frank's noting the similarity of retroperitoneal cystadenomas and cystadenomas of the ovary, glomeruli and renal tubules have, at times, been found in the walls of these cysts. It seems logical to conclude, therefore, that these cysts were mesonephric rather than ovarian in origin. This is the reaction of those who have studied this subject most thoroughly, and the idea of accessory ovary origin has disappeared from the recent medical literature.

Information about solid unattached tumors of this embryological structure began to accumulate at a somewhat later date than that of the cystic tumors and is, even now, very incomplete and unsatisfactory. In 1901 Goebel described a tumor in the left upper quadrant, which upon section presented typical adrenal histology. The adrenal was present on one side of the tumor and was uninvolved. In the same year Chiari and Weise each described an alveolar carcinoma which had arisen independently of adult adrenals. They interpreted the origin from adrenal rests because the cells resembled those of the adrenal. Today, similar tumors found in the kidney would be diagnosed renal cell carcinomas. Verocay in 1906 found a mixed tumor retroperitoneally in the left upper quadrant, which he interpreted as a metastasis from a dermoid teratoma of the ovary. It would appear that the two tumors were independent, because behind the lesser peritoneal cavity would be an unusual place for a metastasis from the ovary and because dermoid teratomas of ovary rarely metastasize. A tumor similar to the one in question, if found in the kidney, would be diagnosed an embryonal tumor from the renal blastema. Chorio-epithelioma-like tumors have been reported several times without relationship to pregnancy, sex or fecundation. They have been found in the bladder, expelled from the vagina of a 3 year old child, in the retroperitoneal region, liver,

TABLE I

Review of Unattached Cystic Tumors of the Urogenital Apparatus Reported in the Literature

Author	Age (years)	Sex	Duration	Location	Histology	Histogenesis	History	Estimated weight (gm.)
Howship (1871). *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	2	F	?	LL	Dermoid teratoma	?	Died	Large
Hosmer (1880). *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	8 mo.	F	?	RL	Dermoid teratoma	?	?	1000
Zweifel. *Zentralbl. f. Gynäk.*, 1888, **12**, 439	18	F	?	LL	Hairy skin	?	Removed, well	?
Bassini. *Zentralbl. f. Gynäk.*, 1889, **13**, 640	37	F	3 yrs.	LL	Ovarian cystoma	?	Removed, well	1100
Frank, E. *Wien. klin. Wchnschr.*, 1894, **7**, 649	37	F	6 yrs.	RL	Ovarian cystoma	Accessory ovary	Removed, well	10,000
Gude, H. (1898). *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	9	M	?	LL	Dermoid teratoma, infected	?	Died	?
Dowd, C. N. *Ann. Surg.*, 1900, **32**, 515	41	F	8 yrs.	LUQ	Ovarian cystoma	Ovarian sequestrum	Removed, well	2000
Göbel, R. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	54	F	27 yrs.	LL	Dermoid teratoma	Bigerminal inclusion	Metastases after 26 yrs.	1000
Seitz, L. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	29	F	3 wks.	RL	Ovarian cystoma	Acessory ovary	Removed, well	4500
König. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	40	F	?	RL	Hair	?	Removed, well	2000

Helbing, C. *Deutsche Med. Wchnschr.*, 1901, **27**, 228	51	M	4 mo.	LL	Papillary adenoma	?	Died	1500
Verocay, J. *Ztschr. f. Heilk.*, 1906, **27**, 176	32	M	4 yrs.	LUQ	Adenocystoma	?	Inoperable	?
Niosi, F. *Virchows Arch. f. path. Anat.*, 1907, **190**, 217	48	F	1 mo.	LLQ	Renal tubules, glands, chorio-epithelium, adrenal-like cells	Wolffian body	Removed, well	1000
Pullmann, W. *Arch. f. klin. Chir.*, 1909, **89**, 357	41	F	1 mo.	LLQ	Ovarian cystoma	Ovarian rest	Removed, well	2000
Oser, E. G. *Arch. f. klin. Chir.*, 1911, **95**, 131	38	F	9 yrs.	LUQ	Ovarian cystoma	Anlage of ovary	Infection and death	1500
Naegeli, T. *Beitr. z. klin. Chir.*, 1918, **110**, 425	22	F	4 yrs.	RLQ	Ovarian cystoma	Supernumerary ovary	Removed, well	1000
Dubs, J. *Arch. f. klin. Chir.*, 1919, **111**, 860	36	F	2 yrs.	RA	Necrotic wall	?	Removed, well	6000
Elder, J. M. *Canad. M. A. J.*, 1920, **10**, 273	2	F	3 wks.	RA	Connective tissue	Wolffian body	Marsupialized, well	?
Schweitzer, G. B. *Monatschr. f. Geburtsh. u. Gynäk.*, 1920, **52**, 171	41	F	6 yrs.	LUQ	Ovarian cystoma	Wolffian anlage	Removed, well	1500
Schweitzer, G. B. *Monatschr. f. Geburtsh. u. Gynäk.*, 1920, **52**, 171	40	F	4 mo.	LUQ	Ovarian cystoma	Wolffian anlage	Removed, well	1700

LUQ = left upper quadrant.
RUQ = right upper quadrant.
LL = left lateral abdomen.
RL = right lateral abdomen.
RA = right abdomen.
LLQ = left lower quadrant.
RLQ = right lower quadrant.

Author	Age	Sex	Duration	Location	Histology	Histogenesis	History	Estimated weight (gm.)
Maury, J. M. *Surg. Gynec. Obst.*, 1918, **26**, 663	28	F	14 mo.	LL	Tubules, glomeruli	Mesonephros	Well	2000
Staehlin, E. *Ann. Surg.*, 1915, **61**, 312	61	M	7 yrs.	RL	Adenocystoma	Mesonephros	Rupture, implants, death	4000
Hinman, F., Gibson, T. E., and Kutzman, A.A. *Ann. Surg.*, 1924, **79**, 762	27 mo.	M	6 mo.	LL	Tubules, glomeruli	Mesonephros	Well	600
Pettis, J. H. *Physician & Surg.*, 1913, **35**, 27	39	F	10 mo.	LUQ	Pseudomucinous cystadenoma	Mesonephros	Died, metastases	700
Moore, F. C. *M. Chron.*, 1902, **4**, 337	38	M	21 mo.	LUQ	Pseudomucinous cystadenoma	Mesonephros	Died	4000
Moore, F. C. *M. Chron.*, 1902, 4, 337	64	M	7 yrs.	LUQ	Pseudomucinous cystadenoma	Mesonephros	Died, metastases	4000
Monprofit. *Gaz. méd. de Paris*, 1904, **4**, 121	?	F	8 yrs.	LUQ	Pseudomucinous cystadenoma	Mesonephros or ovary	Well	5000
Jacquot, C., and Fairise, C. *Rev. de gynéc., Paris*, 1913, **20**, 551	18	F	Indefinite	LUQ	Serous cystadenoma	Mesonephros	Died, peritonitis	3500
Hedinger. *Virchows Arch. f. path. Anat.*, 1902, **167**, 29.	40	F	Found at post-mortem	LL	Serous cystadenoma	Ovary	None	500
Lockwood (1898). *Rev. de gynéc., Paris*, (*Cit.*) 1913, **20**, 551	21	F	2 yrs.	LUQ	Serous cystadenona	Mesonephros	Removed, well	?
Lockwood (1898). *Rev. de gynéc., Paris*, (*Cit.*) 1913, **20**, 551					Serous cystadenoma	Mesonephros	Removed, well	?

Kast, L., (1904). *Rev. de gynéc., Paris,* (*Cit.*) 1913, **20**, 551	55	F	3 yrs.	RL	Serous cystadenoma	Accessory ovary	Died	?
Albarran (1903). *Rev. de gynéc., Paris,* (*Cit.*) 1913, **20**, 551	10 mo.	F	3 mo.	RL	Cystadenoma, Wolffian tubules	Mesonephros	Well	1000
Heyrowski (1908). *Rev. de gynéc., Paris,* (*Cit.*) 1913, **20**, 551	26	M	20 yrs.	RUQ	Pseudomucinous cystadenoma	Mesonephros	Marsupialized, removed 5 yrs. later, recurred 5 yrs. later, died	Massive
Guillemin, A. *Bull. Soc. d'obst. et de gynéc. de Paris*, 1922, **20**, 747	47	F	1 mo.	Pelvis	Cystadenoma	Mesonephros	Removed	1500
Madier, J., and Nathan, M. *Bull. et mém. Soc. nat. de chir.*, 1924, **50**, 200	2½	?	3 wks.	LL	Cystadenoma	Mesonephros	Removed	700
Sacerdote, G. *Arch. ital. di chir.*, 1926, **16**, 122	57	F	2 yrs.	Inguinal canal	Cysts, glomeruli, tubules	Mesonephros	Removed	100
Lawen, A., and Biebl, M. *Beitr. z. klin. Chir.*, 1928, **144**, 505	18	F	1 yr.	RL	Granulation tissue, glomeruli	Mesonephros	Removed, well	700
Romeo, M. *Ann. ital. di chir.*, 1928, **7**, 313	35	F	3 yrs.	LL	Three cavities lined by connective tissue	Mesonephros	Removed	8000
Brouha, M., and Gosselin, O. *Bruxelles-méd.*, 1929, **9**, 831	44	F	5 yrs.	RL	Cystadenoma	Mesonephros	Removed	5000

TABLE II

Review of Unattached Solid Tumors of the Urogenital Apparatus Reported in the Literature

Author	Age (years)	Sex	Duration	Location	Histology	Histogenesis	History	Estimated weight (gm.)
Göbel. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	25	M	5 mo.	LUQ	Adrenal cell carcinoma	Adrenal present, adrenal rest	Operation, death	1500
Chiari, H. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	44	M	6 mo.	RUQ	Alveolar carcinoma	Adrenal rest	Recurrent, operation, death	?
Verocay, J. *Ztschr. f. Heilk.*, 1906, **27**, 176	48	F	2 mo.	RA	Glands and sarcoma	Metastasis from dermoid	Intra-abdominal, hemorrhage, death	2000
Verocay, J. *Ztschr. f. Heilk.*, 1906, **27**, 176	3	F	?	MA	Alveolar carcinoma	Misplaced kidney tissue	Removed, well	1300
Weiss, B. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	27	F	4½ yrs.	LUQ	Alveolar carcinoma	Adrenal present, adrenal rest	Operation, death	2000
Göbel. *Deutsche Ztschr. f. Chir.*, (*Cit.*) 1901, **61**, 1	67	M	3 mo.	LL	Alveolar carcinoma	Adrenal present, adrenal rest	Operation, death	1500
Lubarsch. *Arb. a. d. path. Anat. abt. d. Kgl. Hyg. Anat. z. Posen.*, 1901, p. 230	12	F	?	Uterus	Chorio-epithelioma		Virgin	Large
Bostroem. *Verhandl. d. deutsch. path. Gesellsch.*, 1902, **5**, 212	30	M	2 mo.	ML	Chorio-epithelioma		Died, testes normal	Large

Djewitzki. *Virchows Arch. f. path. Anat.*, 1904, 178, 451	75	F	?	Posterior surface bladder	Chorioepithelioma		Virgin	?
Ritchie. *J. Obst. & Gynæc. Brit. Emp.*, 1904, 4, 65	24	M	10 days	Anterior mediastinum	Chorioepithelioma ? and teratoma	Abnormally secluded sex cell	Suffocated	Large
Marx, H. *Beitr. z. path. Anat. u. z. allg. Pathol.*, 1904, 36, 585	52	M	?	Liver	Chorioepithelioma	Carcinoma of liver	Death	?
Bonney, V. *Tr. Path. Soc. London*, 1907, 58, 9	69	M	3 mo.	Great omentum		Abnormally secluded sex cell	Tapped for 4000 cc. bloody fluid, death	1600
Bock. *Tr. Path. Soc. London*, 1907, 58, 9	12	F	?	Expelled from vagina	Hydatid mole	Fetal placental inclusion	Virgin, 4th menses	20
Askanazy. *Verhandl. d. Deutsch. path. Geselsch. zu Stuttgart.* (*Cf.* Bonney, p. 30.)				Pineal gland	Chorioepithelioma			
Smith, L. H. *Northwest Med.*, 1927, 26, 289	17 mo.	F	2½ mo.	LUQ	Solid round cell tumor	Totipotent cell	Death, metastases	?
Masao, M. *Mitt. u. allg. Pathol. u. path. Anat.*, 1928, 4, 144	39	F	3 mo.	Right kidney	Chorioepithelioma	Hydatid mole ?	Hydatid mole 2 years previous, death, metastases	300
Masao, M. *Mitt. u. allg. Pathol. u. path. Anat.*, 1928, 4, 144	45	F	2 mo.	Right kidney	Chorioepithelioma	Placenta of normal pregnancy	Operation, death, no metastases	600

LUQ = left upper quadrant.
RUQ = right upper quadrant.
LL = left lateral abdomen.
RA = right abdomen.
MA = midabdomen.
ML = midline.

kidney, mediastinum, and pineal gland. Smith recently described a case of a round cell tumor in the kidney region. He did not liken it to the so-called embryoma of the ovary and of the testicle, but he did suggest a totipotent cell as the etiology. The basis for this interpretation was that tumors of the kidney are probably all mixed tumors. Clarke [1] has recently reviewed the theories relating to the histogenesis of tumors containing endometrial-like tissue. He, as well as other authors cited by him, are satisfied that all tumors made up of endometrial-like tissue do not have their origin in implantation of bits of endometrium as described by Sampson. Among several other modes of origin, embryonic Müllerian tissue was suggested. The literature also contains a number of accounts of smooth muscle neoplasms arising retroperitoneally without organ attachment. Could they have arisen from remnants of the Müllerian apparatus? Mixed tumors of mesenchymal origin have also been observed in this region and they occur more frequently than where embryonal structures do not exist. They, too, may have their origin in the urogenital apparatus.

Table III presents the seventeen cases which we have had the opportunity of studying. Fi teen of the cases entered the University Hospital during the last seven years, while two were recognized among the tissues sent to the University by physicians of the state. Sixteen of the tumors were quite independent of the adult genito-urinary organs. In two instances there was invasion of the kidney, which was obviously secondary to a much larger and older tumor of the urogenital fold. While the origin was not so clear in a third case, we believe that an extrarenal origin was the more likely. Case 17 cannot be shown to be urogenital in origin, but it is similar to fibroblastic tumors of mesothelial-lined surfaces such as pleura, synovium and peritoneum, and we have reasoned that it may have had its origin from the mesothelium of the urogenital fold. It had completely surrounded the kidney.

The tabulation comprises a rather heterogeneous group of tumors. Three are cases with epithelial cysts. Two were single cysts and because of the nature of their contents were probably epidermoid. The third was a composite dermoid containing abundant hair and a large flat bone. There were two tumors of typical chorio-epitheliomatous histology. Four massive, friable, solid tumors made up of large round cells were comparable to the so-called embryomas of the

TABLE III

Review of Unattached Tumors of the Embryonal Urogenital Apparatus from 17 Cases in this Report

Case No.	Hosp. No.	Age (years)	Sex	Duration	Location	Histogenesis	Function	Original Diagnosis	History
1	E 1902. 1930	78	M	7 mo.	RUQ	?	o	Infected epithelial cyst	Operation, well
2	B 2061. 1927	41	M	36 yrs.	LUQ	Sex cell	o	Infected dermoid cyst	Death
3	E 8941. 1930	67	M	26 yrs.	LUQ	?	o	Infected epithelial cyst	Death
4	Outside. 1930	26	M	3 mo.	LUQ	Sex cell	o	Chorio-epithelioma	Death
5	B 11067. 1927	26	M	1 mo.	LL	Sex cell	o	Chorio-epithelioma	Death
6	D 7405. 1929	24	M	1½ yrs.	ML	Sex cell	o	Indifferent carcinoma	Death
7	C 5985. 1928	2	F	3 mo.	LUQ	Sex cell	o	Neuroblastoma	Death
8	C 3247. 1929	37	M	1 yr.	ML	Sex cell	o	Indifferent carcinoma	Death
9	59861. 1924	3	F	3 yrs.	LL	Sex cell	o	Indifferent fibrosarcoma	Death
10	Outside. 1930	2	F	?	LUQ	Müllerian apparatus ?	o	Tumor of urogenital apparatus	Inoperable, death
11	C 1737. 1928	70	F	6 mo.	LL	Rete ovarii	o	Adenocarcinoma	Death
12	E 2426. 1930	37	F	1½ yrs.	LUQ	Rete ovarii	o	Adenocarcinoma	Metastases
13	D 232. 1929	48	M	1 mo.	LUQ	Mesonephritic tubules	o	Adrenal cell carcinoma	Removed Jan. 1929, well Dec. 1930
14	E 1661. 1930	51	F	2 yrs.	RUQ	Mesonephritic tubules	o	Urogenital apparatus tumor	Metastases
15	D 6964. 1929	33	F	1 yr.	LUQ	Mesonephritic tubules	o	Adrenal cell carcinoma	Death
16	E 6888. 1930	66	M	3 mo.	RL	Metanephritic tubules	o	Renal cell carcinoma	Death
17	E 2084. 1930	41	M	10 mo.	LUQ	?	o	Fibrosarcoma	Death

LUQ = left upper quadrant. LL = left lateral abdomen. ML = midline.
RUQ = right upper quadrant. RL = right lateral abdomen.

testicle. The histology of Case 11 and Case 12 is identical with two types of carcinoma of the ovary pictured in Ewing's "Neoplastic Diseases." Case 10 was quite similar morphologically to carcinosarcoma of the adult endometrium. Three cases, because of rather mixed histology, including typical Grawitz tumor histology, glomeruli, bone and alveolar carcinomatous areas, we consider were mesonephric in origin. Case 16 reproduces quite accurately adult renal tubule histology. Case 17 was included because it is a fibrosarcoma which may have had its origin in the mesothelium of the urogenital fold.

Case Reports

Case 1. *History:* J. E. (E 1902), a white male of 78 years had pain in the upper right quadrant in September, 1929, a pain which was aggravated by drawing up the legs. Another attack occurred on February 20, 1930, which lasted two days. A third attack occurred recently which lasted a week and was especially severe. He entered the hospital March 13, 1930 after a 15 pound loss of weight. He had had attacks of abdominal pain forty, and again fourteen, years ago.

The patient had some distress when in the dorsal position. There was a large, tender, globular mass which extended from three fingerbreadths below the costal margin up under the right costal margin.

The hemoglobin was 75 per cent, red blood cells 4,280,000, and there were 13,600 to 18,000 white blood cells.

Roentgenological examination showed an incisure of the greater curvature with a niche opposite it indicating gastric ulcer. A shadow in the right upper quadrant was interpreted to be a tumor. The chest was negative. Cystoscopic examination showed a bifid type of pelvis, but it was felt that the mass was independent of the kidney even though the upper calyces of the right kidney were somewhat distorted. At operation cholecystitis and cholelithiasis were demonstrated in addition to an independent large cystic mass. 1600 cc. of brownish material containing a great deal of brownish amorphous material and many cholesterin crystals were evacuated from the cyst. No hair was noted. A piece of cyst was removed for histological study.

Histological Examination: The wall of the cyst was made up of a thick zone of granulation tissue in which were many cholesterin clefts. There was also a heavy infiltration of polymorphonuclear leucocytes. Mononuclear cells and hemosiderin pigment were also present (Fig. 1).

Subsequent Course: The cavity for the most part disappeared and the patient left the hospital with a slight amount of drainage from the operative wound.

Case 2. *History:* J. E. (B 2061), a white male of 51 years entered the hospital with a probable diagnosis of perinephritic abscess. The acute illness began

February 22, 1927, with sharp pain in the lower abdomen. No definite localization of the pain could be pointed out by the patient. There was much bloating and the abdomen was tender. He was taken to the hospital and the local physician thought that the patient might have gall-bladder disease or appendicitis. Temperature varied from 100° to 103° F. He entered the University Hospital February 27, 1927. At that time the pain had localized well over the left kidney region. The patient stated that when he was 4 years old he had a tumor mass in the left side of the abdomen which was quite large. A physician thought that it was attached to the spleen. It disappeared in six months without treatment. He ran a fever and was undernourished until the age of 9, when he began to develop normally. At 21 years he had several hemorrhages, apparently from the gastro-intestinal tract.

The positive points in the physical examination were slight fullness in the left flank and tenderness in the left flank and posteriorly.

The hemoglobin was 87 per cent and the whiteblood cells numbered 17400. The urine had a normal gravity and was free from pathological constituents.

Roentgenological examination showed the left diaphragm to be elevated two intercostal spaces. Air and fluid were demonstrated in an abnormal cavity below the diaphragm. February 28, 1927, the cavity was opened, liberating a cupful of pus which contained considerable detritus. The wall appeared to be discolored granulation tissue. The temperature remained elevated and tenderness beneath the costal margin increased. The patient was reoperated upon March 9, 1927. The stomach and gastrocolic omentum were adherent to the mass. Another cavity of foul pus was opened up. At neither operation was the relationship of the lesion to the viscera, nor the nature of the lesion, ascertained. After the second operation, the tenderness of the abdomen became diffuse and the leucocytes rose to 31,000. March 16, 1927, the anterior wound discharged an amorphous piece of tissue containing many long hairs. Drainage through the anterior wound was profuse and it irritated the skin. A test of the drainage for bile proved positive. The patient died on March 17, 1927.

Postmortem Examination: The body was slightly rigid, icteroid and poorly nourished. The skin about the two surgical incisions, each of which contained drainage tubes, was macerated. The small bowel was agglutinated by fibrin. The peritoneum was lusterless and injected. A large indistinct mass occupied the region of the lesser peritoneal sac. It was multilocular and the walls were made up of granulation tissue. There were firm adhesions to the spleen, stomach and left kidney. 10 cm. above the pylorus where the mass was firmly adherent to the stomach was an ulcer 3 cm. in diameter which had perforated into the mass. All cavities contained hair and one cavity contained a flat bone which measured 3 by 1.5 cm. All organs showed evidences of intravascular infection.

Histological Examination: Sections of the lesion showed a granulation tissue wall which contained many cholesterin clefts and was heavily infiltrated with inflammatory cells, chiefly polymorphonuclear.

CASE 3. *History:* W. S. (E 8941), a white male 67 years old, had had an attack of pain in the upper abdomen in the summer of 1884. The onset was sudden and the character of the pain was designated as knife-like. It came on while working and lasted twenty-six hours. October of the same year there was a similar attack, while a third attack was suffered in December. He has since had "bloating spells" and discomfort in the upper left abdomen. In 1904 he had a severe trauma to the chest. Several months following this, 3000 cc. of pus were removed from the left upper abdomen through a posterior approach. He was very weak and ill at this time and his weight dropped to 98 pounds. Since then, there have been neuralgic pains in the left side. Since 1928, the pain and distress in the upper abdomen have become more severe. In July, 1930, the patient began losing appetite. This was later followed by nausea and then by vomiting. His weight dropped from 140 to 107 pounds.

Except for senility the physical findings were limited to the abdomen. A hard mass extended two fingerbreadths below the left costal margin which was 13 cm. in transverse diameter and extended from the midaxillary line to the lateral border of the sternum. The mass was hard and it descended with respiration.

The urine showed a trace of albumin and a few granular casts. Hemoglobin 84 per cent, red blood cells 4,000,000 and white blood cells 9,800. The blood Wassermann was negative. No free acid appeared in the gastric content even after the administration of histamine.

Roentgenological examination of the colon was negative. The stomach contour was normal and the duodenal cap well outlined. The esophagus arched over the mass which, in turn, retarded the flow of barium into the stomach. Pyelograms showed normal pelves. A large calcified cystic mass was stereoscoped anteriorly to the kidney. Whether or not this mass arose in the kidney could not be determined (Fig. 2). At operation the mass was firmly adherent in the left upper quadrant to the stomach, kidney, spleen and pancreas. An attempt was made to remove it, but the patient died during the operation.

Postmortem Examination: A 1200 gm. mass was found situated retroperitoneally behind the lesser peritoneal sac. The wall was made up of old granulation tissue and was markedly calcified, measuring 0.5 cm. in thickness. There was but one cavity which was filled with brownish, thin material. It appeared to be an old epithelial cyst, the epithelium of which had been destroyed by infection. There was no hair. There were firm adhesions to the stomach, spleen, left kidney and pancreas. These organs were, however, absolutely distinct from the mass. The splenic artery coursed along one surface of this mass.

CASE 4. *History:* A male, 26 years of age, came under observation with the complaint of exhaustion. He had lost 15 pounds in weight. There was indefinite distress in the upper abdomen, which was worse after eating. A smooth tumor was revealed in the epigastrium. Both testicles were in the scrotum and appeared to be normal.

At operation the mass was back of the lesser peritoneal cavity and was ap-

proached through a hole made in the gastro-colic omentum. A tumor which was resilient and dark red was found retroperitoneally. As it could not be removed, a section was taken. Profuse bleeding followed the biopsy and the patient died ten days later.

Histological Examination: The tumor was in every way typical of a chorio-epithelioma.

CASE 5. *History:* H. I. (B 11067), a white male 26 years old, entered the hospital with shortness of breath, hemoptysis (abundant bright red blood), paralysis from the hips down, incontinence of urine and obstipation. The first trouble noted was weakness, in November, 1927. Tubercle bacilli were looked for in the sputum and the report was positive. On December 10, 1927, the patient developed severe backache which kept him awake nights almost constantly. December 18, he developed severe hemoptysis and at this time he was unable to move his left leg. On December 27 his right leg was practically paralyzed. He had incontinence and obstipation since December 22, 1927. His legs recently started to swell.

A dyspneic, emaciated, bedridden and cyanosed patient with hurried speech was observed on physical examination. The temperature was 97° F, pulse 120, and respiration 44. Teeth, throat and tongue were crusted with blood. Blood pressure 100/80. There were sonorous and sibilant râles throughout both chests. Edema extended from the toes to the midabdomen. Each calf measured 38.5 cm. in circumference. All sensations were decreased, ranging from 60 per cent to 0. Abdominal, knee jerk, tendon Achilles and plantar reflexes were absent. A slight flexion of the right thigh was all that the lower extremities could accomplish. No abdominal mass was palpated. The left testicle was not in the scrotum and had not been removed.

The hemoglobin was 55 per cent, and the red blood cells 3,270,000. Polymorphonuclear leucocytes 87 per cent. Blood culture, urine, and blood Wassermann negative.

On roentgenological examination there were large, tumorous opacities of both lung fields (Fig. 3). The skeleton was negative and indirect evidence of intracranial pressure was found. The patient died on Dec. 27, 1927.

Postmortem Examination: The lower extremities and the trunk were edematous and the body was emaciated. The left scrotum did not contain a testicle. Adhesions were present between the left lung and diaphragm. The combined weight of the two lungs was 4000 gm. The lung tissue was practically replaced by large, hemorrhagic masses (Figs. 4 and 5). The terminal ileum contained a few reddish nodules. A hemorrhagic mass which measured 10 x 7 cm. in diameter pushed up the right kidney, encircled the aorta, right ureter and spinal cord. The liver weighed 2600 gm. and contained numerous hemorrhagic nodules. The inferior vena cava was filled with tumor.

Histological Examination: Typical for chorio-epithelioma (Fig. 6).

CASE 6. *History:* C. S. (D 7405), entered the hospital October 11, 1929. He had been well until three months previously, when he had vomiting spells every few days. The vomiting relieved an overcrowded feeling of the abdomen and was not associated with much discomfort or nausea. October 1 he visited a physician, who told him he had a tumor. Recently, he has eaten very little, lost 7 pounds weight and a great deal of strength.

There was a mass in the abdomen which measured 18 by 20 cm. It was firm, fixed and did not move with respiration. Veins were very prominent over the right abdomen but less prominent over the left. Testicles and lymph nodes were negative.

The hemoglobin was 70 per cent, red blood cells 4,000,000 and white blood cells 5,200. Wassermann negative. Blood urea nitrogen 42 mg.

On roentgenological examination the gastro-intestinal tract was negative except for being distorted by a large abdominal tumor. X-ray treatment caused a practical disappearance of the mass in two weeks' time, as far as physical examination was concerned.

He was discharged October 23, 1929, and returned on November 30, 1929. He had gained 26 pounds in weight. The abdominal tumor was almost the same as upon first admission. Weakness of head, neck, leg and arm muscles, which varied markedly from moment to moment developed, and death occurred December 7, 1929.

Postmortem Examination: A massive retroperitoneal tumor extended from the true pelvis to the third lumbar vertebra, which pushed all retroperitoneal structures forward. It was yellowish gray, firm and friable. The mesentery of the small gut revealed a few nodules 3 cm. in diameter. Both ureters were dilated and embedded in the mass. The right ureter showed a demonstrable constriction. The brain was negative grossly and histologically.

Histological Examination: The tumor mass resembled the solid, large, round cell tumor of the testicle.

CASE 7. *History:* M. R. (C 5985), a 2 year old, white female child was brought into the hospital September 22, 1928 because of fever, debility, weakness and pyuria. In July, 1928 the patient became irritable. August, 1928 she was feverish, temperature 102.4° F. Pus and albumin were reported in the urine on August 15, 1928. Since that time irritability increased. There was a desire to sit up and lean forward. She recently lost her vocabulary, and much strength. During the last week she was semicomatose. There was a mass in the left upper abdomen.

White blood cells ranged from 25,000 to 30,000. Nothing abnormal was found in the urine. X-ray after the colon was emptied revealed a large left kidney. Cystoscopy and ureteral catheterization showed a slight cystitis and no function of the left kidney.

The patient was operated upon the day of entrance in the hospital. An incision over the left kidney was made for the drainage of an infected hydronephrosis. As the kidney came into view a tumor involving its middle third was found. The kidney was removed. On histological examination large, usu-

ally round, but at times oblong cells containing distinct nucleoli were present. There was practically no stroma. At times a pseudorosette was seen and a diagnosis of neuroblastoma was made. Death occurred Oct. 11, 1928.

Postmortem Examination: The left kidney was absent, but a smooth mass remained in the retroperitoneal region on the left side which extended from the diaphragm to the pelvis. It measured 18 by 8.5 cm., had a well defined capsule and was slightly adherent to the descending colon. Its cut surface was white, firm and roughly lobulated. The mediastinal glands were involved with the same type of tissue and both lungs showed nodules measuring 2 mm. to 3 cm. in diameter. The liver contained a single metastasis. The left adrenal was absent.

Histological Examination: The histological findings of the neoplastic mass would pass very well for a so-called embryoma of ovary or testicle. This mass was interpreted as primary and the lesion in the kidney was considered metastatic.

CASE 8. *History:* C. R. (C 3247), a white male 39 years old, entered the hospital May 19, 1928, after four days of anuria. He had been well until April, 1928, when his legs from the groin down began to swell and became sore. This lasted one and a half weeks, when the swelling disappeared and the pain subsided with it. In the latter part of April the patient was troubled with nausea and a foul taste in the mouth. For about two weeks previous to admission the patient occasionally vomited very bitter green material. The edema reappeared during the last two weeks. He was able to pass urine normally until May 16 when he passed a very small amount. May 17 he passed only a few drops and anuria developed. A tumor was then found in the abdomen by a physician. There had been a 10 pound loss of weight.

On physical examination the patient lay in bed comfortably but appeared drowsy. The breath had a definite urinous odor. Blood pressure 190/90. The abdomen was rounded and the whole epigastrium above the umbilicus was filled with a hard, nodular, slightly tender, fixed tumor which extended to the rib angle on either side. Anuria was present.

The hemoglobin was 60 per cent, red blood cells 3,900,000 and white cells 8,900. Specimen catheterized from the left kidney pelvis showed a trace of albumin.

The patient was cystoscoped immediately upon admission to the hospital. The bladder was negative. The ureteral catheter could be passed to the pelvis of the left ureter, even though an obstruction was encountered 18 cm. from the ureteral orifice. An obstruction was encountered two-thirds of the way up the right ureter which the catheter would not pass. There were 120 cc. of urine in the left kidney pelvis. The catheter was left in place to drain off the secreted urine. 1 cc. of phenolsulphonephthalein given intravenously did not appear in the urine for forty minutes. Pyelograms showed the left pelvis distinctly hydronephrotic with the calyces clubbed and obliterated. The ureters as outlined swung anteriorly, instead of traveling along the posterior parietes. The right

pyelogram was negative. The left catheter placed in the left kidney pelvis drained 27,000 cc. of urine in forty-eight hours. The blood chemistry determinations were as follows:

Date	Urea nitrogen	Uric acid	Creatinine
	mg.	mg.	mg.
5/19/28	70.3	8.7	17.5
5/21/28	58.0	7.5	12.2
5/22/28	57.4	6.3	10.4
5/24/28	38.3	5.3	5.9
5/26/28	42.7	5.1	3.6
5/28/28	26.3	5.9	2.7
5/31/28	42.0	5.4	3.5
6/ 2/28	53.9	5.8	3.2
6/ 4/28	47.6	5.5	2.9
6/ 8/28	18.2	5.7	1.1

X-ray therapy was given and by June 12, 1928 the tumor had disappeared to palpation. The patient was discharged and on July 19, 1928 returned. There was no palpable tumor at that time. He was given another course of X-ray. October 15, 1928 he was readmitted a second time. He had gained 18 pounds and had returned to regular work. On February 18, 1929 he returned the third time. He had lost 40 pounds in weight, much of his strength and had pains in the chest. The pelvis contained a large mass of tumor and it was felt that there were also metastases to the right chest. Fluid accumulated in the chest, requiring tapping. He became very short of breath and died June 23, 1929.

Postmortem Examination: The right lung, liver and diaphragm were agglutinated by a very cellular, friable tumor. They were removed together and the combined weight was 3,400 gm. There was a large mass in the dome of the liver which continued through the diaphragm and involved most of the lower lobe of the right lung. The liver contained several additional nodules. The inferior vena cava, posterior to the liver, was surrounded by tumor but it was not invaded. The right kidney was markedly, and the left slightly, hydronephrotic. The ureter of the right kidney was obstructed by a scar. Both ureters were surrounded by tumor and there was tumor in the pelvis. One testicle had a nodule in it 2 by 3 cm. which upon section showed nothing but sclerosis.

Histological Examination: The histology of the tumor was in every way similar to the large, round cell undifferentiated carcinoma of the testicle (Fig. 7).

CASE 9. *History:* G. H. (59861), a white girl 3 years old, entered the hospital. She did not walk until two years of age and has never more than hobbled about. A month ago she fell down stairs and has walked but little since then. She cries

out in the night from pain. There was evidence of healed rachitis. Marked fullness in the back extended from the mid-dorsal region to the fifth lumbar vertebra. When standing, the patient bent forward in a curious manner.

She was operated upon July 7, 1924. Incision was made just below the twelfth rib. After separating the quadratus muscle, a pinkish tissue was encountered from which a biopsy was made. The tissue was made up of large, round cells with little stroma. The nuclei varied widely in their ability to absorb dye. Lymphocytes were scattered throughout. Death occurred September 9, 1924.

Postmortem Examination: There was generalized edema and the veins were prominent over the abdomen and about the umbilicus. The prominence of the left lower back measured 10 cm. in diameter. The appendix was bound down by firm, fibrous adhesions. The abdominal contents were pushed aside and to the right by a large retroperitoneal neoplastic mass which measured 15 by 7 cm. in diameter. The left kidney was pushed up, placed on the upper surface of the tumor, but definitely distinct from it. There was a great deal of necrosis but the viable portions were white, granular and friable. The tumor caused pressure atrophy of the tissue about the spinal column and the finger could be passed around the vertebra. The inferior vena cava and right auricle contained tumor. The lung showed metastases 1 cm. in diameter.

Histological Examination: Histological study revealed very large round cells with practically no stroma. Lymphoid cells were scattered throughout.

CASE 10. *History:* The patient was a female child 2 years of age, who had a large mass in the abdomen. At operation the mass was distinctly retroperitoneal, but it could not be demonstrated with certainty whether it arose from an organ or not. A piece of tissue 3 cm. in diameter was removed which was gray, uniform in structure and friable.

Histological Examination: Tubules cut in cross and longitudinal diameters supported by a stroma of round cells such as make up the stroma of uterine endometrium were revealed. Surrounding the foci of glands and stroma were elongated cells, some of which appeared to be smooth muscle cells (Fig. 8).

Postmortem Examination. There was a large, retroperitoneal mass extremely friable and brain-like in appearance back of the lesser peritoneal sac. The spleen could not be identified and it was thought to be completely replaced by tumor. There was a mass of tumor 8 cm. in diameter in the lower pole of the left kidney. Lung metastases were present. It was not interpreted whether or not the large

retroperitoneal mass was primary or secondary to the kidney tumor. Its large size and position, with complete replacement of the spleen, would speak strongly for a primary tumor.

CASE 11. *History:* L. T. (C 1737), a negress, 70 years of age, was in usual health until October, 1927, when she first noted severe shooting pains in the lower back and up and down both legs. Later there was numbness and a prickling sensation. The legs then became weak and on March 18, 1928, she was unable to walk. During this time the patient lost 50 pounds in weight.

Extending from the left kidney region forward, and slightly to the right of the midline, was a tumor filling the whole of the left abdomen. It was fixed posteriorly and moved but little by palpation and respiration. The mass was hard, apparently solid and slightly tender. Strength of the various flexors and extensors of the lower extremities varied from 5 to 25 per cent. Sensations other than pain and thermal were estimated from 30 to 75 per cent. Pain and thermal were normal.

The hemoglobin was 40 per cent, red blood cells 2,500,000. On March 13, 1928 there were 6,200 white blood cells, while on March 27, 1928 they were estimated to be 24,600. Gastric analysis was negative. Rectal examination revealed no pathology. Urine was negative and the stool contained occult blood.

X-ray therapy was given for an inoperable retroperitoneal tumor and it decreased one-third in size. The patient then developed fever, and a leucocytosis of 24,000 and died on March 29, 1928.

Postmortem Examination: There was edema of the lower extremities, more marked on the left. A large mass was found in the left abdomen. The left ureter passed for the most part anterior to the mass, but it was constricted, causing hydronephrosis. The tumor was for the most part in the left lower quadrant. The left psoas muscle, nerves, ureter, ascending colon and the ileum were invaded, but no abdominal organ was primarily involved. There were no distant metastases.

Histological Examination: The tumor was a definite adenocarcinoma with eccentric lumina, a type of tumor frequently seen in the ovary.

CASE 12. *History:* L. A. (E 2426), a white female 37 years of age, complained of severe pain in the left upper quadrant in August, 1928. The pain was usually dull, but occasionally it was distinctly crampy and radiated down the back and left flank. She was hospitalized from July 7, 1929 to February, 1930 because of this, and opiates have since been regularly required. In May, 1929, the patient noted a lump in the left upper quadrant which was near the midline. It was hard but not especially tender and about the size of an orange. It did not respond to X-ray therapy. The Wassermann was found to be positive and 29 "arm shots" and 35 "hip shots" were given without result. Potassium iodide was taken until three months ago. Shortly after the appearance of the abdominal mass, another mass was found in the left axilla. The abdomen was scaphoid except for fullness in the left upper quadrant, beneath which was a

hard, irregular but smooth mass. It extended 8 cm. below the xyphoid on expiration, 12 cm. on inspiration, and the upper limit disappeared under the left costal margin. There was firmness posteriorly over the region opposite the tumor. The left axilla contained a walnut-sized node which was hard, quite freely movable and not tender.

The hemoglobin was 104 per cent, red blood cells 4,680,000 and white blood cells 10,100. The urine revealed nothing abnormal. The Wassermann was 3 plus. Renal function normal.

The gastro-intestinal canal was negative on roentgenological examination except that the stomach was somewhat moulded by a mass in the left upper quadrant. Pyelography revealed a very opaque tumor which stereoscoped anteriorly to the left kidney. The contour of both kidneys and pelves was normal (Fig. 9).

At operation a mass 4.5 by 2.5 by 1.5 cm. was obtained from the axilla. It was made up of three separate but very firm nodules. The largest nodule was gray and granular and contained mucoid material. Encircling this nodule was a mass containing much gritty material, and the third nodule was completely calcified except for being divided into lobules by white, fibrous tissue.

Histological Examination: The gray tissue was epithelial, the cells arranged in acini with eccentric lumina. The calcified tissue was made up of epithelial rete structures which were supported by embryonic-appearing connective tissue. In this stroma calcified masses were found which resembled corpora amylacea and tended to pass into the lumina of the rete structures (Figs. 10 and 11).

CASE 13. *History:* O. R. (D 232), a healthy appearing white male of 48 years, noted a mass in the left upper quadrant in December, 1928. An attack of pain in the left lower back in November, 1928 is the only symptom that could be elicited from the patient, which might have had a bearing on the condition. The important findings in the physical examination were limited to the abdomen. With the patient in the recumbent position, the mass extended from a point midway between the umbilicus and symphysis up under the costal margin. The upper pole could be grasped on deep inspiration. Laterally, the tumor extended from the midline to the anterior axillary line. The contour felt lobular and the tumor mass was not tender. Back of the tumor under the costal margin a rounded mass thought to be kidney was felt. Splenic dullness seemed normal. A tympanitic colon could not be demonstrated over the mass. The movement of the left costal margin was limited and the tumor moved with the margin. When the patient stood erect the tumor dropped practically to the symphysis and when the patient rolled on the right side, it fell well to the right of the midline.

The urine contained 8 pus cells per high-power field. The Wassermann was negative. Stool examination showed a 1 plus test for occult blood. There were 8,650 white blood cells and 4,970,000 red blood cells. Differential count revealed no pathological cells or abnormal percentages. The hemoglobin was 85 per cent.

Fluoroscopic and roentgenological examinations of the colon suggested no intrinsic bowel pathology, but did suggest a retroperitoneal tumor, posterior

to the transverse colon. Stereoscopic pyelograms showed the left kidney to have normal contour. The pelvis and the upper part of the left ureter were slightly dilated and the ureter was pushed somewhat to the right as if the tumor were back of the kidney and ureter. The spleen was visualized and appeared normal in size. What was taken to be the tumor was at the lower pole of the left kidney. When the tumor was moved there was movement of both tumor and kidney but the displacement of the kidney in no way equaled that of the tumor (Figs. 12 and 13). The function of both kidneys was impaired.

The patient was operated upon January 16, 1929. There was a grapefruit-sized mass overlying the space between the stomach, spleen and transverse colon, the latter being pushed down. It was most intimately attached to the pancreas but the left kidney, though pushed down, was entirely unattached. The mass was removed.

On gross examination the tumor mass weighed 660 gm. It was very well encapsulated and in the capsule many large vessels were observed. A few cysts several centimeters in diameter protruded above the surface. When they were incised a bloody fluid escaped. On cross-section 90 per cent of the area was dull, red and lusterless, indicating dead tissue. The remaining 10 per cent consisted of cream-colored, granular, friable tissue which appeared viable. From these areas sections were taken.

Histological Examination: Sections showed cells arranged in cords with large, thin-walled blood vessels between. There were whorls of these cells which called to mind a renal glomerulus. The individual cell did not contain much lipoid material. It was felt at the time, from the position and histology of the tumor, that it was an adrenal carcinoma (Fig. 14).

Subsequent Course: The patient had a satisfactory postoperative course and was discharged on February 12, 1929. He was given three X-ray treatments over the area from which the tumor was removed. On December 30, 1930, approximately two years after the operation, he was well.

CASE 14. *History:* M. F. (E 1661), a white female, 51 years of age, had had intermittent pain in the upper abdomen for two years. The first attack was in the left upper quadrant, but all attacks since have been in the right abdomen. After these attacks large amounts of urine were passed which did not contain pus, blood or stones. There have been five such attacks in all. There has been no jaundice or clay-colored stools. There was slight rigidity in the epigastrium and 5 cm. above the umbilicus a point of tenderness was encountered. The palpable mass which was 10 cm. in diameter and slightly to the right of the umbilicus was movable and markedly tender. It was definitely distinct from the gall-bladder.

The hemoglobin was 70 per cent and the white blood cells were 5,900. There was only slight acid in the gastric juice after histamine administration. Enzyme action of the duodenal juice could not be said to be abnormal. The content contained a considerable amount of bile. Wassermann and Kahn tests were negative. The Graham Cole test showed the gall-bladder outline but concentration of dye was estimated 50 per cent normal.

Roentgenological examination of the gastro-intestinal tract showed the duodenum pushed up by a mass immediately before or behind it. Pyelograms showed the kidney outlines and contour normal, with a mass of different density mesial to the kidney. At operation there was a small amount of clear fluid in the peritoneal cavity. No tumor of intra-abdominal organs was found on exploration. A tumor lay to the right of the vertebrae at the level of the head of the pancreas, the main mass of which was distinctly retroperitoneal. It was lobulated, gray, granular, friable tissue with a flat surface. There was a small nodule where the mass reflected onto the duodenum. It was considered inoperable and a biopsy was taken which consisted of a piece of tissue 2.5 by 1.5 by 1 cm. It was gray, granular, friable and lobulated, with little stroma.

Histological Examination: Parts of the tumor were indistinguishable from the so-called adrenal cell carcinoma of the kidney, while other parts were distinctly alveolar. The cytoplasm of the latter cells contained no visible lipoid material. Still other areas were made up of large, round, embryonic cells (Figs. 15 and 16).

CASE 15. *History:* L. S. (D 6964), a white female 33 years old, had a knife-like pain in the left thigh and anterior groin since June, 1927. November 5, 1928 an ovarian cyst the size of a cocoanut was removed, but no histological examination was made. Since January, 1929 there has been a cough with hemoptysis. January 25, 1929, the patient experienced a sudden pain in the back which traveled to the inguinal region and down the inner side of the left thigh. It lasted fifteen to thirty minutes, and four hours later there was a chill and fever with marked diaphoresis. Similar pains were frequent during the week following. Since September 1, 1929, there has been cough with production of foamy yellow-white sputum, considerable pain in the left chest and dyspnea. 250 cc. of straw-colored fluid were removed which caused an increase in the discomfort. September 25, 1929, pain in the right chest required strapping.

On physical examination a well developed and well nourished, dyspneic patient, propped up in bed, was observed. Respirations were rendered shallow by pain. The left costal margin was immobile and the right moved but slightly. The upper left chest was tympanitic and the base was flat. Breath sounds and voice sounds were increased over the left upper chest while the lower chest was silent. The right back was dull to percussion and the left was flat. Every third heart beat was a right ventricular extra-systole. Two abdominal scars from an appendectomy and oöphorectomy were found. The left upper quadrant resisted deep palpation. The left costal margin, the anterior axillary line and a point halfway between the xyphoid and the umbilicus outlined a mass in the left upper quadrant. Respiration caused slight movement of the mass. It moved more, however, during palpation of the left back. There was tenderness with muscle spasm in the left upper quadrant and the mass seemed attached to, or firmly pressed against, the left costal margin. The Kernig test was posi-

tive and produced pain in the left flank. Temperature varied from 98° to 102.8° F, pulse from 84 to 134 and respiration from 20 to 32. Blood pressure was 125/85. The left chest was tapped for 550 cc. of turbid fluid which showed no organisms. The hemoglobin was 63 per cent and the white blood cells 13,600. The Wassermann was negative. Five urine examinations revealed no pathology. There were numerous right ventricular extra-systoles.

Roentgenological examination showed the left lower half of the chest opaque and the excursion of the right diaphragm was limited. Numerous tumorous opacities were scattered throughout the upper part of the left lung and the entire right lung. The heart and the mediastinum were displaced to the right. Some of the lesions were thought to be metastatic neoplasm. Barium enema filled a normal colon. There was a large mass of osseous density in the left upper quadrant which did not move freely with respiration. Pyelograms showed a normal kidney contour and a normal pelvis configuration. The mass seemed quite definitely distinct from the kidney (Fig. 17). Death occurred Nov. 8, 1929.

Postmortem Examination: Both lungs were studded with grayish, firm nodules. The larger masses were soft in their central portions and were miliary-sized to 3 cm. in diameter. The hilum nodes were replaced and enlarged by tumor. The liver revealed disseminated nodules of neoplasm which varied from miliary-sized to 5 cm. in diameter. The tumor mass measured 17 by 12 by 18 cm. and was distinct from the kidney. In the central portion of the upper pole of the tumor was a calcified mass which measured 6 by 2 by 2 cm. There was considerable necrosis. The left kidney was atrophic and weighted 90 gm., and the right kidney weighed 130 gm.

Histological Examination: The tumor showed extensive bone formation. The cancellous spaces were filled with round tumor cells. The part of the tumor not containing bone was made up of cords of cells which appeared somewhat similar to adrenal cells. They were rather small, however, and contained no free lipoid (Figs. 18 and 19).

CASE 16. *History:* W. T. (E 6888), a white male 68 years of age, entered the hospital August 27, 1930, complaining of frequency (every twenty minutes day and night). Thirteen weeks previously the patient strained himself while lifting a heavy load. At this time he felt something give way in the groin. Soon afterward the scrotum became swollen and has since been tapped nine times, only to fill up quickly again. At this time frequency began which was followed by severe terminal tenesmus. He has had constant suprapubic pain, associated with intermittent excruciating pain which radiated from the left flank to the penis. Three of these attacks during the last thirteen weeks required morphine for relief. He has recently had severe dyspnea and palpitation on exertion.

Physical examination revealed senility and cardiac failure. Blood pressure 195/104. The hemoglobin was 75 per cent, red blood cells 4,000,000 and white blood cells 7,400. The Wassermann and Kahn tests were negative. The blood urea nitrogen was 40 mg.

A cystogram showed a tumor on the right side extending from the fundus to the base of the bladder. Cystoscopy revealed infection of the bladder with a large sessile tumor. X-ray examination of the chest suggested carcinomatous metastases. X-ray treatment was applied with no result. On September 23, 1930, the patient developed phlebitis of the right leg. Two days later there was a chill followed by temperature of 102° F, and leucocytosis of 16,900. His general condition became gradually worse and death occurred on December 27, 1930, following shortly after a right hemiplegia.

Postmortem Examination: The mediastinal lymph nodes were enlarged by gray, granular, neoplastic tissue. Similar tissue extended along the bronchi. The head of the pancreas lay over a large, retroperitoneal mass the center of which was at the level of the renal veins. The tumor extended from the diaphragm to the bladder, surrounded and partially constricted the aorta and followed along the calyces to replace about half of the left kidney. The right ureter and pelvis were dilated and surrounded by tumor and the bladder wall was invaded.

Histological Examination: Renal tubules were very accurately reduplicated (Fig. 20).

CASE 17. *History:* N. K. (E 2084), a white male 65 years old, entered the hospital complaining of pain in the lower abdomen and back, vomiting, poor appetite and loss of weight. Pain was first noted throughout the lower abdomen in September, 1929. January, 1930, pain developed in the left testicle and on March 10, 1930, a small irregular lump appeared at the upper pole of the right testicle. The patient had lost 25 pounds during the last three months.

Physical examination revealed a large mass in the left upper quadrant which descended slightly with respiration. The urine was negative. The hemoglobin was 75 per cent, red blood cells 4,000,000, and the white blood cells 8,400. The blood urea nitrogen was 25 mg., uric acid 6 mg., and creatinine 1 mg.

The tumor was found retroperitoneally in the left upper quadrant. An abscess containing 15 cc. of pus was opened in the region of the fundus of the stomach. On March 29, 1930 the patient began to raise purulent sputum, became increasingly weaker and emaciated. Death occurred April 13, 1930.

Postmortem Examination: There was a large, retroperitoneal mass 15 by 12 by 8 cm. which completely surrounded the left kidney, the lower pole of which had been somewhat replaced by tumor. The left kidney showed hydronephrosis. There were neoplastic implants over the peritoneum, small metastases to both lungs and a single small metastasis to the liver. The right testicle contained a small hydrocele. There was a staphylococcic septicopyemia.

Histological Examination: The histology was that of a fibrosarcoma. It resembled quite closely fibroblastic neoplasms of the pleura, synovial surface and meninges.

Histogenesis and Clinical Considerations

Two points arise when tumors come up for consideration. One, the question of histogenesis, is chiefly of academic interest. The recompense here must, for the most part, come from the satisfaction and security which goes with understanding. This question is based on fragments of truth which were derived from interval observations of a continuous embryological process. Gaps are left which must be filled in by interpretation. Application of these embryological processes exposes even wider and more frequent gaps in our knowledge of histogenesis of tumors. The other question of how to recognize tumors and what to expect of them with and without various types of interference is the practical point. Both the pathologist and the clinician are interested in this latter consideration.

Histogenesis is a much disputed question because it is largely based upon morphology. Cells do not always reproduce their kind accurately and the dispute wages about the point of what metaplastic potency may be imputed to a certain cell at a given stage of embryological differentiation. Some authors are very strict in the degree that a cell may change in form or function even within the same germ layer. Others seem to think that, in rare instances, a cell of one germ layer may mutate into the cell of another germ layer. Again, metaplasia, both progressive and retrogressive, is quite generally assumed to have a wider range in neoplasms than in injury and repair lesions. We do not wish to submerge ourselves in this abyss of controversy. We propose to accept the quite widely taught histogenetic explanations for the tumors arising within the adult genito-urinary organs and apply them to explain tumors which are unattached but of similar histopathology. In a few instances, histopathology, anatomy, embryology and comparative embryology have led us to suggest another explanation for the histogenesis than the one commonly accepted. Finally, we will compare and endeavor to correlate the histogenetic explanations offered for tumors attached and unattached to adult organs when a different histogenesis is offered for each.

Table IV will be of material aid in guiding us in this consideration.

Histogenesis: Histogenesis of simple cysts, with or without hair, may concern any one of several type cells. During embryonic life the genito-urinary structures and the ectoderm are practically in appo-

TABLE IV

Tumors of the Urogenital Apparatus

(A) *From Nephrogenous Tissue with Inclusions*

Histology	Attached	Unattached	Histogenesis
Adrenal-like cells, glomeruli, bone, tubules and alveoli	Embryonic renal cell tumors	This series In the literature	Mesonephros
Cords, adrenal cells	Adrenal cell tumors	In the literature	Adrenal cell
Adult renal cells, adult renal tubules	Adenoma, adenocarcinoma	This series	Adult renal cell
Glomeruli, rich stroma, tubules	Embryonal adenosarcoma	In the literature (?)	Renal blastema
Smooth muscle	Leiomyoma, leiomyosarcoma	In the literature	Müllerian tissue(?)
Fibroblasts	Fibroma, fibrosarcoma	In the literature	Mesothelium ?
Fibrous cartilagenous fat and bone	Mixed tumors	In the literature	Mesothelium ?
Epithelial cyst	Epithelial cyst	This series In the literature	?
Syncytial and Langhans cells	Chorio-epithelioma	This series In the literature	Sex cell

(B) *Genital Tissue with Appendages and Inclusions*

Syncytial and Langhans cells in cords	Chorio-epithelioma	This series In the literature	Sex cell
Large round cell	Embryoma	This series	Sex cell
Glandular arrangement, eccentric acini, calcareous deposit	Adenocarcinoma	This series	Rete cells
Solid, teratomatous	Teratoma	None	Sex cell
Cystic, dermoid teratoma	Dermoid cyst	This series In the literature	Sex cell
Epithelial cyst	Epithelial cyst	This series In the literature	?
Alveoli, tubules, uterine mucosa stroma, smooth-muscle	Endometrioma, adenosarcoma	This series	Embryonic Müllerian tissue
Adult endometrium	Endometrioma	In the literature	Adult Müllerian tissue
Cervical epidermoid carcinoma	Epidermoid carcinoma	None	Adult Müllerian tissue
Smooth muscle	Leiomyoma, leiomyosarcoma	In the literature	Adult Müllerian tissue
Striated muscle	Rhabdomyoma, rhabdomyosarcoma	None	Sex cell (?)
Cystadenoma	Cystadenoma, pseudomucinous	In the literature	Mesonephros
Cystadenoma	Cystadenoma, serous	In the literature	Mesonephros
Fibroblasts	Fibroma, fibrosarcoma	This series In the literature	Mesothelium?

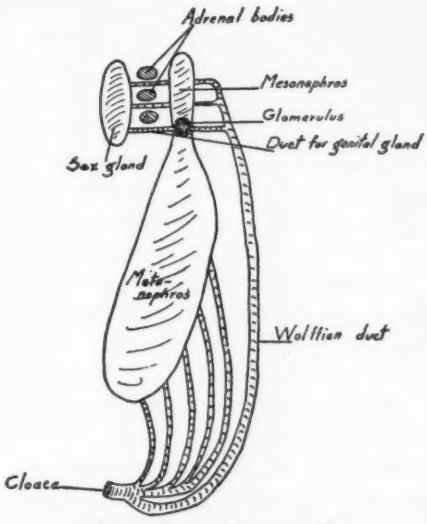
sition. When muscles and vertebrae form, the genito-urinary structures are pushed forward. At this time bits of ectoderm may be carried forward with the genito-urinary apparatus. This would give an explanation for simple dermoids in such organs as kidney, ovary and testicle, as well as for simple dermoids and epithelial cysts not attached to these adult organs. Again, we have epithelial structures extending from the fourth cervical vertebra to the pelvis which may not completely degenerate and which may give rise to epithelial cysts. We do not believe that it is assigning too much progressive metaplastic potency to these cells in considering that they may account for some of the simple dermoid cysts.

The solid and dermoid teratomas are quite generally conceded to arise from totipotent sex cells when found in the ovary or testis. We found no solid teratomatous masses, but dermoid teratomas arefound not only in our series, but also in those described in the literature. They are quite similar to dermoid teratomas of the adult sex glands and we assign to them an aberrant sex cell histogenesis.

When one cell in a teratoma grows with rapidity, it may metastasize and reproduce a simple tumor of the type cell which began rapid proliferation. It seems that the small, well formed teratoma first grows and then has a quiescent period, after which some particular element in that small teratoma again takes on growth and metastasizing tendencies. In this manner chorio-epitheliomas, embryomas, voluntary muscle and smooth muscle tumors from sex cells are explained when the tumors arise within the genital organs. Commonly, small teratomas of the testicle have been found which have given rise to a massive metastasis to the retroperitoneal structures. We have noted a well developed dermoid teratoma of the ovary which was about 1 cm. in diameter. It was still contained within a follicular cyst. These small teratomatous masses are not frequently found in malignant retroperitoneal tumors of the urogenital apparatus. They may be lost in the massive tumor or replaced by the rapidly growing, more vigorous malignant cell. We can see no objection to assigning sex cell histogenesis to similar embryonal tumors, *viz.*, the so-called embryomas, dermoid teratomas, chorio-epitheliomas, and certain smooth and striated muscle tumors, when they are found not attached to the sex glands.

Here we should mention again the disputed origin of the sex cell. If we accept the segregation of the sex cells during the morula [2,3]

stage of the embryo, which is the more widely accepted theory, we must permit a wider distribution than if the sex cell developed after the embryo took on its definitive morphology,[4] as provided for in the second theory. It is obvious that the cell may get lost in its migration to the dorsal mesenchyme, or that some cells may be carried to various parts of the body when the embryo takes on its final form.



DIAGRAMMATIC DRAWING II

Urogenital system of salamander

We may, in this way, account for chorio-epitheliomas in such places as the liver, mediastinum and pineal gland.

We may dismiss the pronephros by stating that we have found no information about it, unless this structure accounts for some of the simple dermoids found in the mediastinun. There also seems to be no information on unattached tumors from the very embryonic renal blastema. Solid tumors of the mesonephros and the adrenal are either from the same ontogenic [5] tissue or not far removed in phylogeny.[6] It is believed by some that the adrenal develops from the cross tubules of the mesonephros, while others are equally certain that the adrenal arises from a separate invagination of the mesenchyme by celomic epithelium.[6] In the salamander (see Diagrammatic

Drawing II) the former explanation is true. Either explanation would indicate the close embryological relationship of these two structures. The metanephros arises from a continuation of the nephrogenic cord caudad to the mesonephros. It is contiguous then with the mesonephros. For these reasons it will be well to consider the histogenesis of these tumors as members of the same family.

Before the time of Grawitz, the small yellow, and even the more rapidly growing large yellowish, tumors of kidney were considered tumors of renal cell origin. The writings of Grawitz so nearly convinced the medical world, that it was infrequent that an epithelial neoplasm of the kidney was diagnosed as anything but an adrenal cell tumor. Legitimate doubt again arose because of the large number of renal tumors which had alveolar arrangement throughout, and a portion of still others was distinctly alveolar. It is true that the cells were, at times, similar and frequently resembled adrenal cells, but this distinct alveolar arrangement was not easily assigned to adrenal cells. The explanation of origin from renal tubules which were arrested in development now holds sway. Our cases which resembled adrenal cells, but in which glomeruli, bone and alveolar structures were found, developed high in the abdomen independently of the kidney. They developed above the level of the metanephric portion of the nephrogenous cord and from a portion which would correspond to the site of origin of the mesonephros. Embryologically, the mesonephros is more closely related to the adrenal than is the metanephros. Might not the adrenal-like masses found near the epididymis and the masses of adrenal-like tissue found near the hilum of the ovary of infants, as described by Marchand, be in no inconsiderable number of instances remnants of the cross tubules of the mesonephros? It would seem more logical to conclude that they were fragmented pieces of the mesonephros which had been torn away when the testis or ovary began its descent, than to suppose that they came from a more mesially situated adrenal. Is it not likely that mesonephric remnants may easily be included in the metanephros since these tissues are contiguous and may even overlap? Lastly, some of the unattached tumors which resembled the adrenal in structure, but where the adrenal was uninvolved, were high in the abdomen and had a distinctly tubular structure. Individuals who feel that this type of tumor is not of mesonephric origin have these observations to explain.

It would seem that the diagnosis of adrenal cell tumor would be warranted only when the histology was adrenal-like throughout, or the tumor manifested the function of the adrenal cortex. When all is said and done, we anticipate that there will be members of this group so nearly alike that an assignment of histogenesis cannot be made with certainty. To the more definitely tubular tumors, which at times are papillary, the adult renal cell is assigned for histogenesis. We had one such case in our series of unattached tumors. It arose from the lower part of the nephrogenic cord and was first recognized as a bladder tumor because it had invaded this organ. This caudad origin in the nephrogenous cord substantiated the accepted theory of histogenesis.

The cystic tumors of the embryonic mesonephros, when they are found unattached, resemble the serous and pseudomucinous cystadenomas of the ovary. There is, at times, an attempt at glomerulus formation in the walls of the cysts. The explanation quite widely accepted is that they are remnants of the Wolffian duct and that the two types of cysts vary only in the function of the epithelial cell lining the cyst wall. Natural history of these tumors and similar tumors arising within the ovary does not warrant any further distinction. The ovarian pseudomucinous and serous cystadenomas are frequently interpreted as arising from ingrowth of the epithelium covering the surface of the ovary and are, therefore, closely related to the epithelium of the Graafian follicle. It is possible that cysts may arise in this way also, but the former explanation seems to us the more likely and the better substantiated.

Whether or not the rete structures are part of the sex gland, or a continuation of the cross tubules from the mesonephros which connect the sex gland with the Wolffian duct, is not certain. Two of our cases, we believe, are from rete structures. Roessle and Wallart [7] reported a case of hyperplasia of the rete structures associated with infantilism. There were nodules of adrenal-like tissue attached, which we consider were part of the contiguous cross tubules of the mesonephros. The rete structures resembled very closely the psammomatous portion of the tumor in Case 12 of our series. Both epithelial cells and arrangement, as well as the stroma, are similar. This led us to the opinion that the cell masses containing the numerous eccentric acini found in another portion of this psammomatous tumor are a more abortive attempt at the formation of rete structures.

No explanation has been given for these types of tumor when they occur in the ovary.

The Müllerian apparatus will now be considered. Conservative pathologists have not been satisfied with the explanation of Sampson for all endometrial-like tumors occurring in aberrant locations. The theories of histogenesis are well summarized by Clarke.[1] When tumors of this sort occur only along the course of the embryonal Müllerian apparatus it seems more logical to believe that they had their origin from that structure, than to explain that they passed through this particular part of the peritoneum without leaving a scar. This would explain endometriomas, either glandular or epidermoid, in the rectovaginal septum and retroperitoneally. It also opens a likely explanation for the frequency of leiomyomas retroperitoneally. The tumor in Case 10 of our series resembles very closely the so-called adenosarcoma of the endometrium.

The potency of mesothelium has been appreciated since it has been established that synovial and pleural tumors produce bone, fat, fibrous tissue, angiomatous tissue and glandular tissue. We assume that this might account for many of the mixed tumors with no particular characteristics which will associate them with a more definite embryonal structure. Such tumors are found both within and without the adult genito-urinary organs.

Clinical Facts Common to Tumors of this Series: Clinically, there are points of general interest which pertain to all tumors of this series. Age is not a discriminating feature because they may occur throughout the life span of an individual. Frequency is also of minor importance since there has been only slightly less than one tumor reported annually in the world's literature. We might state here that the chances are not few that many are wrongly interpreted in the archives of the various clinics. The left side, and especially the left upper quadrant of the abdomen, is the most usual site for these tumors. There is no explanation found for this fact. There seems to be a natural division into solid and cystic tumors. The cystic tumors occur much more frequently in females. There is a striking difference in the results from treatment. Prognosis after removal of the pseudomucinous and serous cystadenomas, if they have not as yet invaded surrounding structures, is good. The treatment of dermoid cysts is hampered by their attachment to surrounding structures because of the inherent nature of this tumor to cause adhesions. The

results from removal of the solid tumors are very disappointing. There is a ray of hope even here, since the patient in Case 13 of our series is alive and well two years after removal of the tumor. This tumor was very movable, not having mingled with the surrounding tissue. Perhaps we shall in the future be able to diagnose more tumors at this stage of development. This will be more probable if urologists will make a special point of looking for these tumors in the routine examination of the genito-urinary tract. The filling of numerous cysts by secretion in a cystadenoma markedly increases the size of the mass which is likely to attract the attention of the patient and the physician early, before the tumor has mingled with the adjacent retroperitoneal tissue. Small retroperitoneal solid tumors of like age may remain quiescent for years and not be found because of their size. Even cystic tumors have been known to metastasize after twenty-six years of quiescence. These tumors must all be considered potentially malignant. The capsule is sooner or later invaded; there is mingling with surrounding tissues, implantations on the peritoneum may result, and finally more distant metastases occur. It will be noted that this natural history is the history of similar tumors in the adult urogenital organs.

Unless metastases have taken place we have only a tumor in the abdomen, with its associated discomfort, to consider. These tumors are usually quite massive. Cystoscopy with pyelograms, followed by stereoscopic plates, has been of the greatest value. A normal pelvis and a normal kidney contour with a massive retroperitoneal tumor renders the diagnosis of a urogenital apparatus tumor very likely. The stereoscopic study gives one some idea of the relative position of the kidney and of the mass. If the tumor is movable, the question of whether it moves independently of the kidney may be of value. The injected kidney pelvis may be considered a fixed point and the tumor may be moved by palpation as shown in Figs. 12 and 13 from Case 13. Incidentally, roentgenological examination of the gastro-intestinal tract will usually show distortion from the expansive growth of the tumor. Tumors of the gastro-intestinal tract are usually not so large and globular. A cyst (lymphangiomatous, dermoid or epithelial) however, may arise between the leaves of the mesentery. Tumors of the adrenal, mesonephros, or rete structures may collect calcium in the form of psammoma bodies, amorphous calcium, or bone. The metastases in one of our cases

contained psammoma bodies. The metastasis in this case was unusual in that there was a very mixed histological picture in addition to the calcification. An infected cyst will give the clinical picture of a retroperitoneal abscess which at times resembles a perinephric abscess. These tumors seem to arise deep in the retroperitoneal structures when they are not pushed forward by the adult kidney. In three of our cases there was paresis of the lower extremities, and in two of these the tumor invaded between the laminae of the vertebrae.

Points of Practical Interest about Individual Tumors of this Series: A few points of interest about individual tumors may deserve separate consideration. There are many possibilities, retroperitoneally, for simple epithelial cysts. We have epithelial structures of various sorts extending from the fourth cervical vertebra, where the pronephros begins, to the pelvis. They may be lined by epithelium and may also contain hair and immature hair follicles. The capsule is usually quite thick and there are adhesions to the surrounding tissues and organs which cause difficulty in removal. The thickness of the wall, coupled with a large amount of brownish, grumous content, should lead one to suspect a preformed cyst in contradistinction to a chronic abscess, at the time of operation. Hair in the cyst content renders the diagnosis secure.

Dermoid teratomas are similar except that they contain multiple cysts with many well defined hair follicles. The contents of the cysts, in addition to being grumous, are greasy. Hair is usually abundant and coarse. Bone in the tumor, as shown in the roentgenograms and at the time of operation, is very significant. When these teratomas become infected, granulation tissue covers the walls of the various cysts and the cavities are filled with hair and puriform material. The natural history is similar to dermoid cysts of the ovary. Our case had a history of a mass in the left upper quadrant for thirty-six years. This tumor most likely arose from a sex cell as the genital fold extends from the first dorsal vertebra to the pelvis. Furthermore, if we accept the theory that sex cells are segregated in the morula stage of the embryo, we must permit a wider distribution of this tumor than is indicated by the extent of the genital fold.

The massive undifferentiated epithelial tumors (embryomas), have a natural history very similar to a metastasis from the testicle.

They become very large, degenerate and metastasize by invading veins. They are soft, friable tumors. Ureters are surrounded and occluded, leading to anuria, as found in one of our cases. They, at times, respond well to X-ray treatment. The tumor being of sex cell origin may be found elsewhere than along the course of the genital fold, but because of its indifferent nature it probably would not be recognized in aberrant locations.

Chorio-epitheliomas have been reported in the liver, the kidney, the mediastinum and the pineal gland. Askanazy's case of pineal chorio-epithelioma was accepted by Bonney upon examination of the material. Even though we must be cautious in diagnosing a tumor which is typical, as a chorio-epithelioma, on morphology alone, when the tumor is found in such remote places as the pineal gland we must admit that the early segregation of the sex cell permits such wide distribution. The tumor is usually soft and dull red in color. The natural history is that of chorio-epithelioma of the uterus, testis or ovary.

We have not as yet observed any solid tumors from the pronephros. The solid tumors of the mesonephros, the metanephros and the adrenal may be considered as a family. The natural history of these tumors is similar to adrenal cell carcinoma and renal cell carcinoma of the adult kidney. They are likely to be yellowish in color. Necrosis is frequently a prominent feature in them. They manifest a great tendency to invade veins and grow along them as tumor thrombi. By the time they are diagnosed they usually have metastasized. The histopathology is typical adult adrenal cortical cells in cases of adrenal cell tumors. There may or may not be adrenal medullary cells or excessive adrenal cortical function. The mesonephric tumors have adrenal-like cells. There is an alveolar arrangement of cells or there is mixed alveolar and adrenal-like histology. At times, there is an attempt at glomerulus formation. Tumors of the metanephros are likely to arise from the caudad portion of the nephrogenic cord. They may invade the bladder and kidney. The histology is, at times, very like adult renal tubules. Calcification and ossification occur more particularly in the adrenal and mesonephric tumors.

Another tumor closely related to the mesonephric tissue and the adrenal is the so-called psammoma of the ovary. Evidence has been set forth to show that this type of tumor may come from the rete

cells. This type of tumor is occasionally mixed with a tumor composed of masses of epithelium, each mass containing numerous eccentric acini which may be an attempt to reproduce rete structures. This type of tumor is easily recognized. Our case (Case 12) showed metastases to the axilla. These metastases showed both the adenocarcinomatous areas with psammoma bodies and epithelial nests containing numerous acini.

Tumors from the mesonephros may be cystic. Here, we refer to the so-called serous and pseudomucinous cystadenomas. The natural history of these tumors in the ovary is so well known that space is hardly warranted to present a natural history for similar unattached tumors. They may grow to weigh 20,000 gm. They may become malignant after twenty-six years of quiescence. Extremely large cystadenomas may be ruptured as a result of strain upon the abdomen. The favorable cases for surgical interference are of this group.

Leiomyomas occur retroperitoneally unattached, as well as within the kidney. They are somewhat more malignant than leiomyomas of the adult uterus, but are otherwise similar. A rather friable mixed tumor was found in the region of the left kidney which had invaded the kidney and had the histological picture of an adenosarcoma of the endometrium. Its invasiveness resembled the similar tumor occasionally encountered in the adult uterus. More benign tumors reduplicating adult endometrium are found in the rectovaginal septum, and as time goes on we predict that they will also be found retroperitoneally along the course of the Müllerian apparatus. One of us (G. H. H.) has on one occasion seen a carcinoma in the rectovaginal septum which resembled a carcinoma of the cervix. Such are the possibilities of the Müllerian apparatus.

Fibrosarcomas as well as tumors containing fibroblastic tissue, fat and cartilage, are found retroperitoneally. They usually grow to large size before metastases occur.

Summary and Conclusions

1. Seventeen retroperitoneal tumors which were not attached to adult urogenital organs are reported.

2. All tumors reported are similar to tumors which arise in the adult urogenital organs.

3. Retroperitoneal tumors collected from the literature integrated with the material of this paper have shown that almost all tumors which occur in adult urogenital organs may occur free along the course of development of the urogenital apparatus.

4. The concept that they arise from remnants of the urogenital apparatus is the most logical explanation of their histogenesis.

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DESCRIPTION OF PLATES

PLATE 141

FIG. 1. Case 1. Photomicrograph showing a thick wall of acutely inflamed granulation tissue in which many cholesterin clefts are present. × 130.

FIG. 2. Case 3. X-ray showing large unilocular calcified cyst which stereoscoped anterior to the kidney. History of forty-six years of upper abdominal pain.

1

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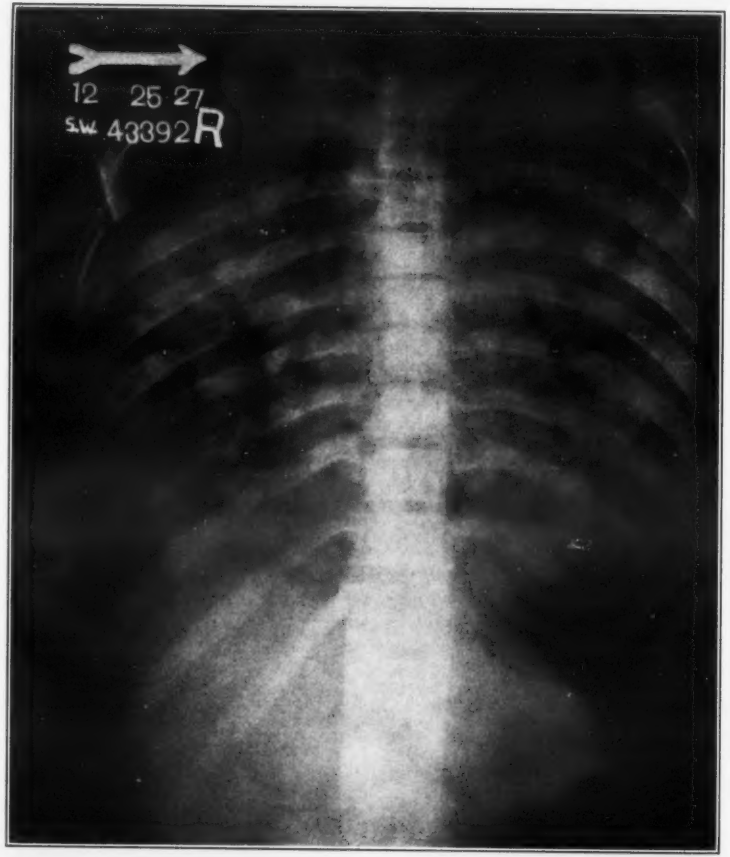
Massive Unattached Retroperitoneal Tumors

PLATE 142

FIG. 3. Case 5. X-ray showing chorio-epitheliomatous metastases in the lung of a twenty-six year old male with a primary retroperitoneal chorio-epithelioma. See Figs. 4, 5 and 6.

FIG. 4. Case 5. Massive hemmorhagic metastases in the right lung from a large primary retroperitoneal chorio-epithelioma. See Figs. 3, 5 and 6.



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Massive Unattached Retroperitoneal Tumors

PLATE 143

FIG. 5. Case 5. Cut section of lung showing massive hemorrhagic pulmonary metastases from the tumor shown in Figs. 3 and 4.

FIG. 6. Case 5. Photomicrograph showing typical chorio-epithelioma. See Figs. 3, 4 and 5. × 130.

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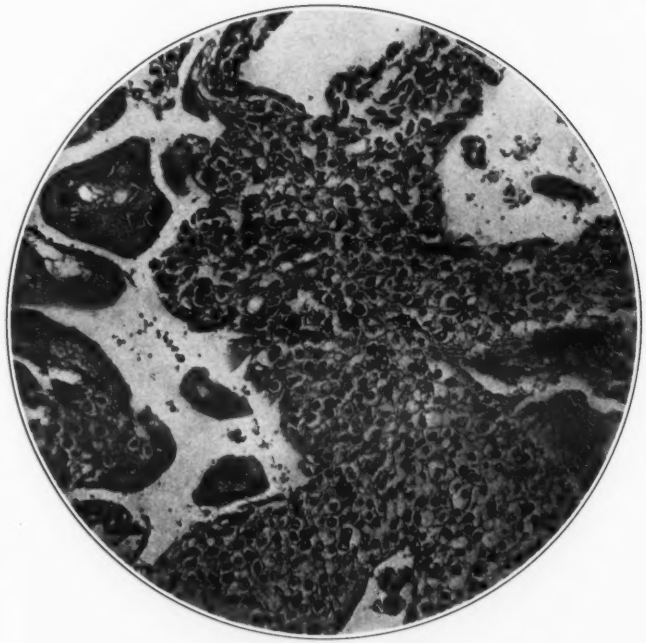

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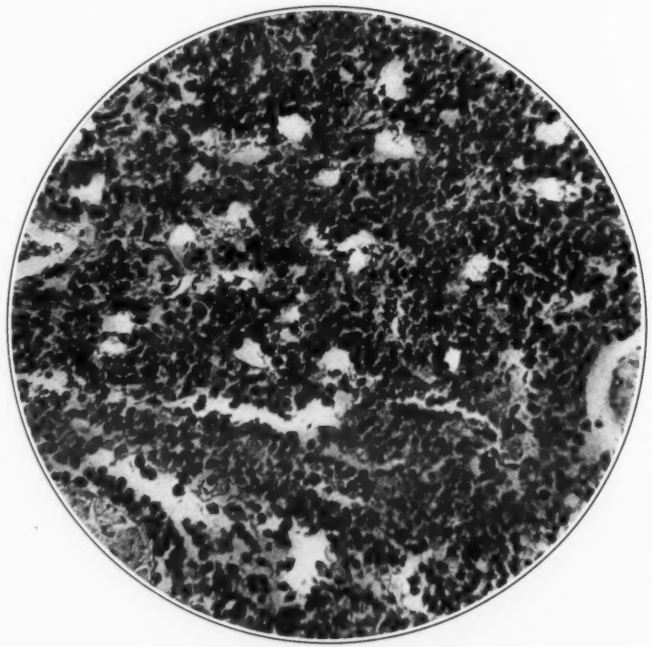
Massive Unattached Retroperitoneal Tumors

PLATE 144

FIG. 7. Case 8. Photomicrograph showing large round cells with slight adenomatous differentiation. Similar to the so-called embryoma of the testicle. × 130.

FIG. 8. Case 10. Tubular structures and small round cell supporting stroma with what appears to be smooth muscle at periphery. Reminiscent of uterine endometrium. × 130.



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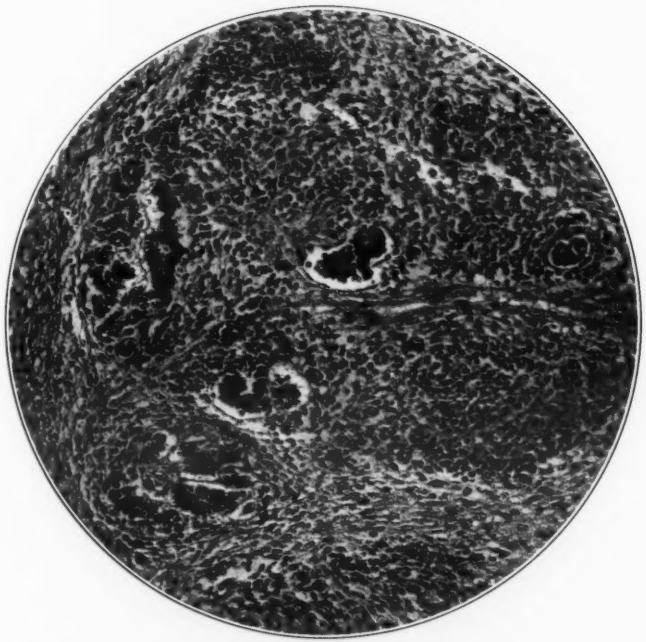

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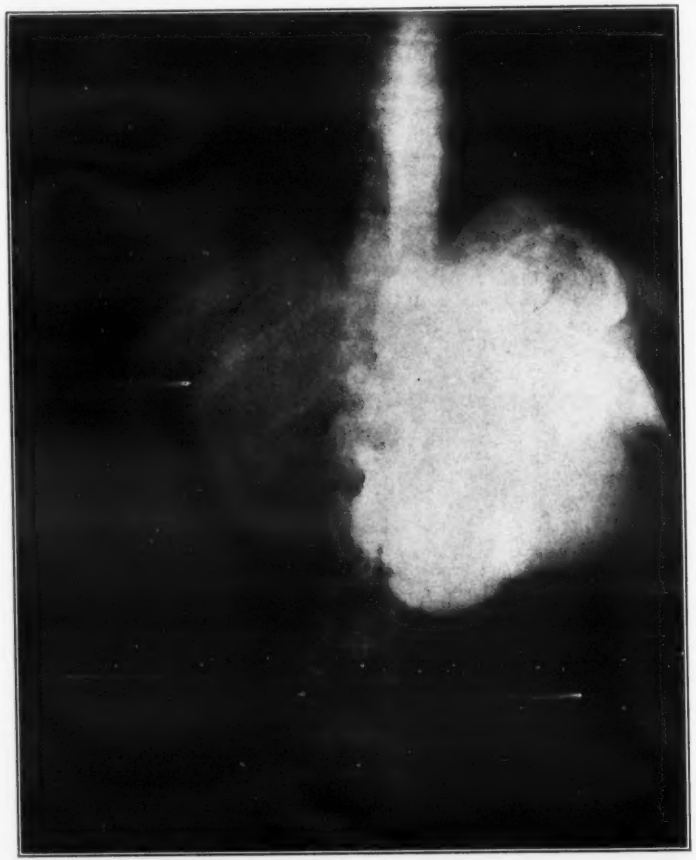
Massive Unattached Retroperitoneal Tumors

PLATE 145

FIG. 9. Case 12. X-ray showing large calcified mass anterior to left kidney. See Figs. 10 and 11.

FIG. 10. Case 12. Photomicrograph showing large calcareous masses in the tumor shown in Fig. 9. Similar to Fig. 286, a carcinoma of the ovary, in Ewing's "Neoplastic Diseases." See Figs. 9 and 11. × 130.



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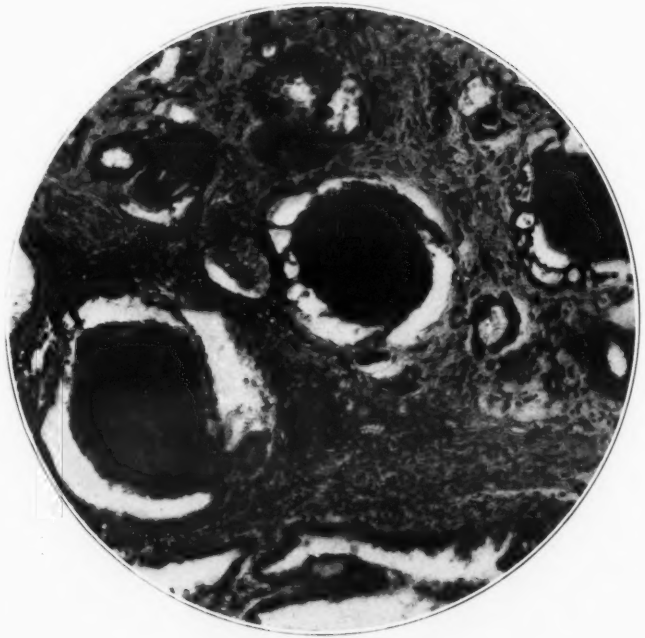

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Massive Unattached Retroperitoneal Tumors

PLATE 146

FIG. 11. Case 12. Photomicrograph showing adenocarcinoma with eccentric acini. See Figs. 9 and 10. × 130.

FIG. 12. Case 13. X-ray showing tumor in left upper quadrant. See Figs. 13 and 14.

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Massive Unattached Retroperitoneal Tumors

PLATE 147

FIG. 13. Case 13. X-ray showing displacement of tumor by palpation. It moves independently of the kidney. See Figs. 12 and 14.

FIG. 14. Case 13. Photomicrograph of tumor shown in Figs. 12 and 13, showing adrenal-like cells and arrangement with attempts at glomerulus formation. × 130.

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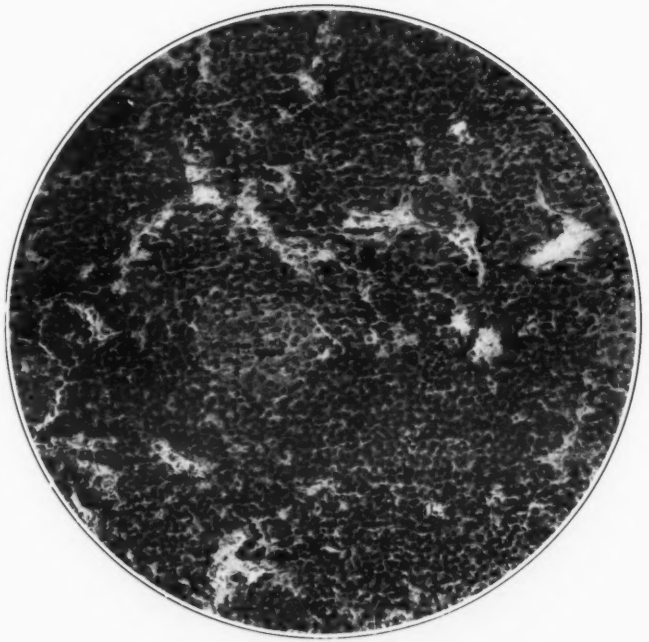

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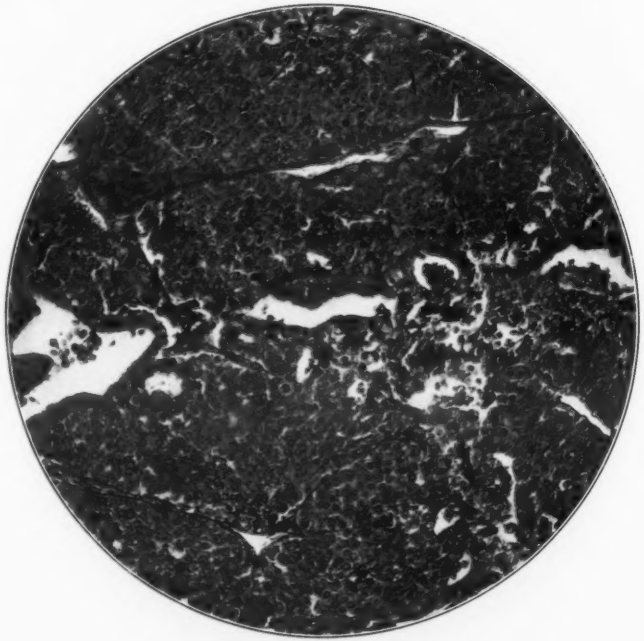
Massive Unattached Retroperitoneal Tumors

PLATE 148

FIG. 15. Case 14. Photomicrograph showing solid and alveoli arrangement of cells. × 130.

FIG. 16. Case 14. Note typical Grawitz tumor. × 130.



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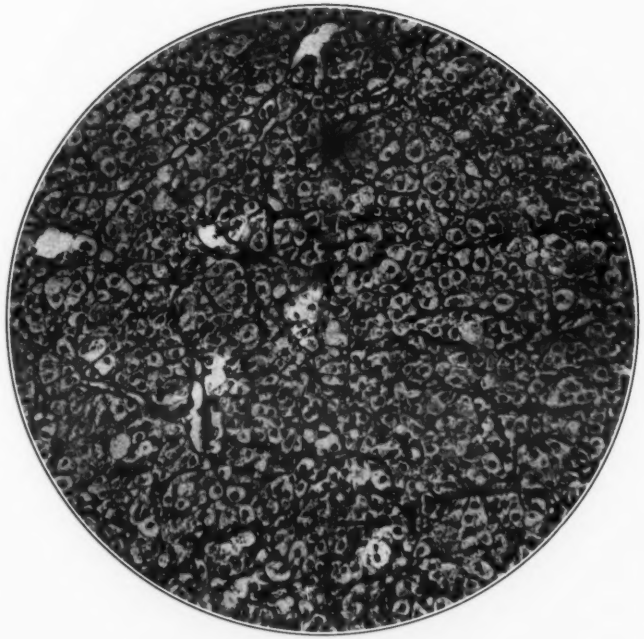

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Massive Unattached Retroperitoneal Tumors

PLATE 149

FIG. 17. Case 15. X-ray showing calcified mass high in the left upper quadrant. See Figs. 18 and 19.

FIG. 18. Case 15. Photomicrograph of tumor shown in Fig. 17 showing adrenal-like arrangement of cells. × 130.

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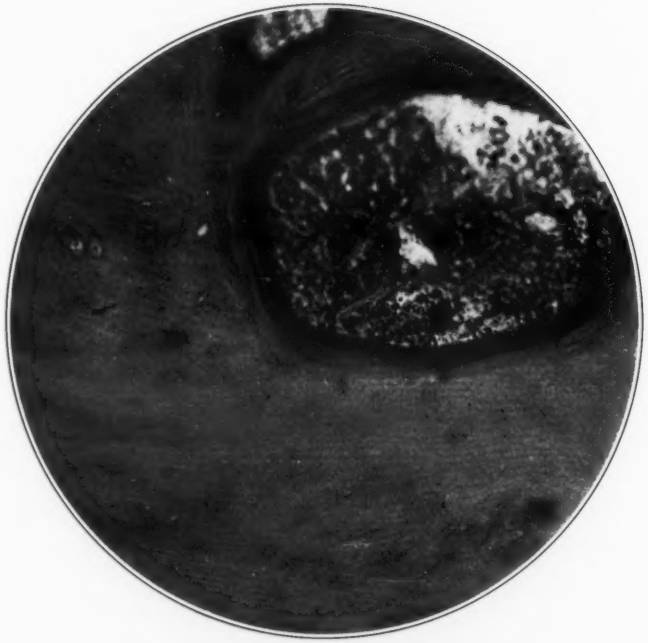
Massive Unattached Retroperitoneal Tumors

Plate 150

Fig. 10. Case 15. Photomicrograph from same tumor as Fig. 18, showing active bone production. × 130.

Fig. 20. Case 16. Note quite accurate reduplication of metanephritic tub ·les. × 120.



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Massive Unattached Retroperitoneal Tumors

PAPILLIFEROUS TUMORS OF THE THYROID GLAND AND OF ABERRANT THYROID TISSUE *

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Papilliferous tumors of the thyroid have formed a heterogeneous group, the common feature of which has been gross or microscopic papilliferous epithelial hyperplasia. Such tumors have constituted slightly less than 10 per cent of the malignant epithelial tumors of the thyroid, according to the reports of Müller and Speese, Simpson, Graham and Wilson.

After Wölfler described solid and cystic forms of papilliferous tumors of the thyroid in 1883, little more was done to define the types and to correlate structure with gross characteristics until 1925, when Graham distinguished three kinds of malignant papilliferous tumors. Numerous varieties of tumors have been characterized as papilliferous, and opinions have differed as to their malignancy. Low and Zehbe minimized the significance of papilliferous structure, and because that type of hyperplasia is so common to the thyroid they did not favor distinguishing such tumors from adenocarcinomas. However, Low did observe that papilliferous cystadenomas should be recognized as a type of tumor prone to repeated recurrence, rather than to metastases.

Ehrhardt believed the papilliferous tumors to be a subtype of cylindrical cell carcinoma of the thyroid, but held that the cystic form stood midway between the malignant and benign tumors. This latter opinion was shared by Halstead, Verebly, Müller and Speese, and Plessner, although in some instances the generalization was applied to solid, as well as to cystic forms.

Wegelin recognized a solid and cystic form of true papilliferous tumor, and a papilliferous type of macrofollicular adenoma which he excluded from the papillary group. Simpson did not specify any particular type of papilliferous tumor but agreed with Wegelin that their malignancy was most commonly limited to local invasion or metastasis to neighboring lymph nodes. Neither related the struc-

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ture of the various types of papilliferous tumors to their gross characteristics. This relation was suggested by Graham who stated that there are three groups of malignant papilliferous tumors: (1) the papilliferous cystadenocarcinoma which is locally malignant; (2) the malignant adenoma exhibiting papilliferous differentiation, which may metastasize widely; and (3) the papilliferous adenocarcinoma not arising in an adenoma, the malignancy of which was not defined.

If the malignancy of these tumors varies with their structure, the significant types should be accurately described. Twenty-eight papilliferous tumors of the thyroid were available for study from the Institute of Pathology of Western Reserve University. There have been at least 149 cases reported, not including the material studied in the various reviews and general treatises in which case protocols were not given. The protocols of seventy-four were considered adequate for the purpose of classification.

The material studied was as follows: Papilliferous tumors of the thyroid gland (twenty-four cases from Lakeside Hospital * and forty cases from the literature), and papilliferous tumors of aberrant thyroid gland tissue (four cases from Lakeside Hospital and thirty-four cases from the literature). Tumors described in published case reports were classified according to their pathological descriptions and illustrations which, in some instances, were not in accord with the diagnoses given them by their authors.

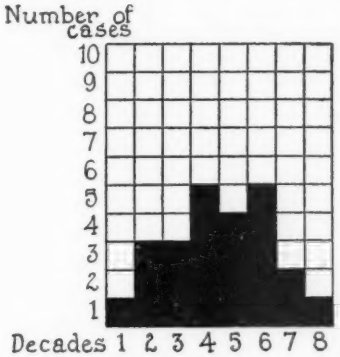
Papilliferous Cystadenoma

Twenty-seven papilliferous cystadenomas of the thyroid gland or of aberrant thyroid tissue were studied. Twenty-three of them were selected from the literature as having sufficiently detailed pathological descriptions or illustrations for the purpose of classification.† These were encapsulated, cystic tumors which were par-

* The authors wish to express their appreciation to Doctors Crile, Cutler, Goff, Holloway, Sloan and Weidlein for permission to publish cases operated upon by them, and to Dr. Allen Graham for information regarding the postoperative survival of many of the patients.

† Papilliferous cystadenomas of thyroid gland or of aberrant thyroid tissue included in this study were reported by Binney, Jores, Kapsammer, Kocher (Case 20), Leech, Smith and Clute (Cases 1, 2 and 3), Low (Cases 1, 5 and 6), MacLennan, McGlannan (Cases 2 and 4), Moritz and Bayless (Case 3), Müller and Speese (Case 1), Payr and Martina (Case 1), Plauth, Pollard, Reynier (Case 1), Verebly (Case 4), Wegelin (Case 1), and Zahn and Züllig (Cases 2 and 5).

tially or entirely filled by macroscopic papillae arising from the lining (Fig. 1). Ten were in the thyroid gland and seventeen in aberrant thyroid tissue. They occurred with slightly greater frequency in males than in females (15:10). The age distribution at operation is shown in Text-Fig. 1. The average preoperative duration of the tumors was fourteen years, in the twelve instances where that information was available. There were no significant differences in age or sex distribution between such tumors arising in the thyroid and those arising in aberrant thyroid tissue. They varied



TEXT-FIG. 1. Age incidence by decades of papilliferous cystadenomas based on age at time of operation or autopsy.

from less than 1 cm. to 10 cm. in diameter, and the largest tumors were in most instances those of longest known duration.

Both unilocular and multilocular cysts were described, and in the latter some of the locules were smooth-lined while others were papilliferous. In such tumors areas of intact or only partially degenerated adenomatous tissue were seen (Fig. 3). Great variation in structure was observed in some of the multiple tumors of aberrant thyroid tissue in which colloid adenomas, cystadenomas and papilliferous cystadenomas coexisted. The papillae varied in size and complexity, were usually covered by cuboidal or columnar epithelium, and were supported on an abundant fibrous stroma, which was commonly the seat of hyaline degeneration and edema, to produce rounding of the free ends (Fig. 1). Although nuclei were seen at the free ends of cells (Langhans) and cells were in some instances cylindrical (Ehrhardt) neither feature was characteristic. Coalescence of papillae

was uncommon. Calcification and lymphoid infiltration of stroma and capsule were common. Follicular differentiation of papilliferous epithelium was uncommon and portions of such tumors comprised of colloid-containing follicles were regarded as rests of the original non-papilliferous adenoma. Usually the contents of the cysts were thin and sanguinous.

The transitional forms seen in multiple tumors of aberrant thyroid tissue suggested that this type of neoplasm developed in adenomas which were the seat of cystic degeneration.

Papilliferous Cystadenocarcinoma

Thirty-five papilliferous cystadenocarcinomas of the thyroid gland, or of aberrant thyroid tissue were studied. Twenty-seven of these were selected from the literature as having sufficiently detailed pathological descriptions or illustrations to permit of classification.* These malignant tumors were cystic and papilliferous in the gross and the only essential differences between them and the benign papilliferous cystadenomas were their invasive growth and metastasis to cervical lymph nodes. In twenty cases the tumors originated in the thyroid gland, and in fifteen in aberrant thyroid tissue. The age at time of operation is shown in Text-Fig. 2.

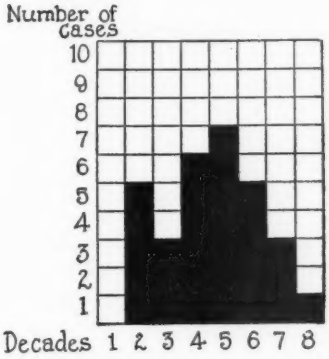
As in the papilliferous cystadenomas there was a greater number of cases operated upon in the fourth, fifth, and sixth decades than in any other three decades, but the difference was not marked and here, as in the preceding group, the long preoperative existence of the tumors indicated an earlier age onset than is shown in Text-Fig. 2. The preoperative duration of the tumors was about the same as that of the papilliferous cystadenomas. Twenty-four were in females and six in males.

Follow-up observations were available on fourteen patients. Eight of them showed recurrences in three years or less, but in six there were no recurrences in from three to nine years. In two cases the tumors were large, the operations were deemed palliative, and

* Papilliferous cystadenocarcinomas of the thyroid or of aberrant thyroid gland tissue included in this study were reported by Barker, Berger, Billings and Paul, Carranza, Ehrhardt (Case 1), Günzler, Hinterstoisser (Case 3), Hueck (Case 5), Hughes (Cases 2 and 6), Kamsler, Langhans (Cases 1, 2 and 3), Leech, Smith and Clute (Case 4), Moritz and Bayless (Cases 5 and 6), Payr and Martina (Case 3), Plessner, Pool, Rühl, Simpson, Schrager, Smoler, Verebly (Cases 2 and 3), Wegelin (Cases 3 and 5), and Züllig (Case 1).

postoperative X-ray treatment was given. One of these was free from recurrence in six and one-half years and the other in nine years after operation. In some of the so-called recurrences of papilliferous cystadenocarcinomas of aberrant thyroid tissue the possibility of the development of independent new tumors could not be excluded, since multiple tumors were described by Barker, Billings and Paul, Hinterstoisser, Leech, Smith and Clute and were seen in two cases studied by us.

Although these tumors were cystic, there were instances in which the luxuriant growth of papillae in some of the locules and the



TEXT-FIG. 2. Age incidence by decades of papilliferous cystadenocarcinomas based on age at time of operation or autopsy.

scirrhous character of the advancing margin were responsible for the macroscopic appearance of solidity. They were commonly multilocular, and their contents often hemorrhagic. Papillae varied in size and shape, exhibited a tendency to coalesce, and in the more actively proliferating areas were delicate with great multiformity of the covering epithelium. In every case there was capsular invasion, in nine extension into the adjacent cervical muscles or trachea, and in twelve there were metastases to lymph nodes of the neck. In no instance was blood vascular invasion seen. The advancing margin of the tumor was usually characterized by dense fibrosis (Fig. 2) which extended into the adjacent non-tumorous tissue. The invasion was accomplished by the peripheral development of small, solid islands of epithelial cells which formed atypical follicles. Beneath the peripheral zone there was papilliferous infold-

ing into the small follicles (Fig. 2 and Fig. 7). As the center of the tumor was approached the follicles were larger and the papillae more luxuriant, until there was a final coalescence with the major cyst cavity, or contribution of new locules to it. Transitional stages were seen between papilliferous cystadenoma and papilliferous cystadenocarcinoma. Arbitrary distinction depended upon the presence or absence of transcapsular infiltration.

That the papilliferous cystadenocarcinomas developed from cystadenomas seemed probable because of the presence of transitional forms and also because in cases having multiple tumors of aberrant thyroid tissue the coexistence of cystadenoma, papilliferous cystadenoma and papilliferous cystadenocarcinoma was observed. The metastases were papilliferous and the larger ones were cystic. The papillae developed in small atypical follicles and there was evidence of secretory activity with distention of the follicles to cystic proportions.

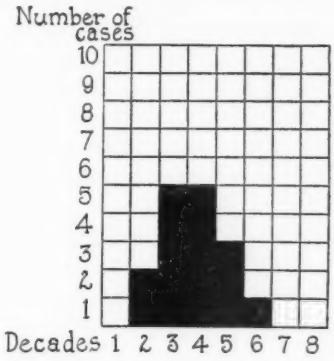
Papilliferous Adenomas

Seventeen papilliferous adenomas of the thyroid gland or of aberrant thyroid tissue were studied, twelve of which were selected from the literature.* Fifteen developed in the thyroid gland and two in aberrant thyroid tissue. Fourteen were in females and three in males. The age incidence at time of operation is seen in Text-Fig. 3. These tumors, three of which were included in Wölfler's original description of papilliferous newgrowths of the thyroid, were not primarily papilliferous, as were the papilliferous cystadenomas or cystadenocarcinomas. The papilliferous character was microscopic and was due to diffuse or focal intra-acinar epithelial hyperplasia. It was similar to that commonly seen in association with Graves' disease and did not go on to the formation of cysts filled with macroscopic papillae.

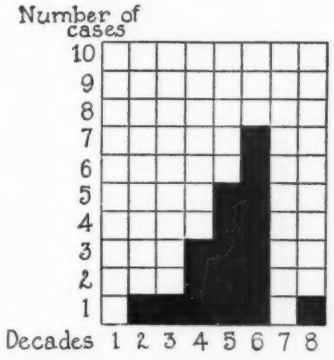
Martini described a tumor in which there was a subcapsular zone of cystic follicles into which the epithelium extended in folds and papilliferous excrescences, but both his description and illustrations indicated that the change was not truly papilliferous, but simple

* Papilliferous adenomas of thyroid have been reported by Kocher (Case 19), Langhans (Case 5), Low (Cases 2 and 4), Martini, Moritz and Bayless (Case 4), Verebly (Case 1), Wegelin (Case 4), Wischmann, Wölfler (Cases 1, 2 and 3), and Züllig (Case 4).

hyperplasia. Papilliferous hyperplasia into cystic follicles was seen in Wölfler's Cases 1 and 3, and Züllig's Case 4. The papillae of such tumors were small, relatively simple, and covered by uniform columnar epithelial cells. They were supported by a delicate stroma which did not exhibit degenerative changes. Calcification, hemorrhage,



TEXT-FIG. 3. Age incidence by decades of papilliferous adenomas based on age at time of operation.



TEXT-FIG. 4. Age incidence by decades of malignant papilliferous adenomas based on age at time of operation or autopsy.

lymphocytic infiltration and fibrosis were not characteristic, although Wischmann described such a tumor in which there was so much calcification that he chose to call it an "adenoma cylindrocellulare papilliferum psammomatosum." In no instance was there capsular or vascular invasion, or metastasis.

Papilliferous Malignant Adenomas

Nineteen papilliferous malignant adenomas were studied, twelve of which were from the literature.* These were solid, more or less completely encapsulated tumors in which papilliferous hyperplasia was usually microscopic and consisted focal inof diffuse or trafollicular epithelial proliferation. Malignancy was manifested by invasion of capsule, or by blood or lymph vascular metastases. Sixteen of the tumors originated in the thyroid gland and three in aberrant thyroid tissue. Eleven of the patients were females and seven were males. The age incidence at time of operation or autopsy is shown in Text-Fig. 4.

In this group the clinical histories usually indicated the presence of a goiter or tumor many years prior to operation or death, with a recent preoperative or ante mortem acceleration in growth. In three instances the tumors were so large and showed such extensive local invasion that origin in an adenoma could not be identified. In several of the tumors there were macroscopic cystic areas, usually degenerative in character and not sharply defined. With few exceptions, these tumors displayed papilliferous structures similar to those of the preceding group (papilliferous adenomas), (Fig. 6). Portions of the tumors in which follicular structure was manifest exhibited intrafollicular papilliferous hyperplasia of epithelium. The advancing margins were not always papilliferous. The case of McCarthy and Karsner was an exception, in that the pulmonary metastases, as well as the primary tumor, were papilliferous and the papillae were not of the simple delicate variety characteristic of simple hyperplasia, but were stout arborescent structures with abundant stroma and focal calcification. In one of our cases the tumor was predominantly adenocarcinoma although there were true papilliferous areas, and in one of the intravascular tumor masses papilliferous differentiation was apparent. The tumor reported by Wohl cannot be unequivocally diagnosed a papilliferous malignant adenoma. In four instances the metastases were papilliferous (Kocher, Halstead, Hudson, McCarthy and Karsner).

* Such tumors have been reported by Fedeli (Cases 1 and 3), Halstead (Cases 2 and 3), Hudson, Kocher (Cases 14 and 15), Langhans (Case 4), McCarthy and Karsner, Wegelin (Case 7), Wohl, and Zehbe.

In four of the seven cases studied by the authors, and in five of the twelve cases from the literature, malignancy was manifested by blood vascular invasion. Local lymph nodes were involved in six instances. Of the eight patients followed, four were living and well in six years or more, one was dead in six years, one in three and one-half years and two lived less than a year.

Papilliferous Carcinoids

Case Reports

Case 1. A white male, 54 years of age, gave a history of goiter for three years with symptoms of Graves' disease for two years. Thyroidectomy was performed. In the lower pole of the right lobe there was a small, pale, scirrhous lesion which measured about 1.5 cm. in diameter, not encapsulated, but sharply defined. Its cut surface was gray, uneven, gritty and of non-uniform density. Microscopically, it was comprised of discrete but atypical and often elongated, non-colloid-containing acini distributed through an abundant, dense fibrous stroma. The stroma was continued beyond the parenchyma and intervened between it and the adjacent gland tissue. There was calcification and diffuse lymphocytic infiltration of the stroma. Some of the follicles were large and many of them were filled by one or several branching papillae which were covered by single or multiple layers of epithelium which varied greatly in size and shape of cells and nuclei. The surrounding gland tissue was colloid-containing and nodular. The patient was living and well six and one-half years after operation.

Case 2. White female 52 years of age. Goiter since puberty. A large (115 gm.) nodular goiter was removed. In the upper pole, in the non-tumorous portion of the gland, there was a small, pale, densely fibrous area which was of non-uniform density and structure and which contained no colloid (Fig. 4). This lesion was of irregular outline, and its surface merged with the fibrous stroma of the surrounding colloid-containing gland tissue without sharp distinction. One surface was attached to, but had not invaded the capsule. Microscopically this area consisted of atypical, labyrinthine acini into which there was papilliferous invagination of lining epithelium. The papillae were both simple and complex and showed some secondary acinar differentiation. The epithelial cells lining the acini and

covering the papillae were larger, more acidophilic and manifested greater multiformity of cells and nuclei than in the adjacent colloid-containing thyroid gland. There were occasional mitoses and nuclear monstrosities. Numerous small islands of undifferentiated epithelium were distributed through the stroma which was abundant, densely fibrous, diffusely infiltrated by lymphocytes and which extended out into and merged with the interstitial tissue of the adjacent gland. The small solid nests of epithelium showed advanced degenerative changes and atrophy, as though being replaced by the proliferating stroma. The patient was living and free from recurrence thirteen years after operation.

CASE 3. White female, 29 years of age. Graves' disease for about two years. Right lobectomy was performed. The lobe contained two adenomas and was generally involuted with some diffuse increase in fibrous connective tissue. At the upper pole, attached to but not invading the capsule, was an irregularly shaped, non-encapsulated mass 7 mm. in diameter, which was pale, fibrous and gritty on section. Microscopically, small and large compressed atypical acini were distributed through a dense, fibrous stroma. There was intra-acinar proliferation of simple and branching papillae. Both acinar and papilliferous epithelium were atypical and differed from epithelium of surrounding thyroid in size and staining qualities of cells. The cells were large, polymorphous, and many exhibited degenerative changes. The stroma was abundant, the seat of focal calcification, and diffusely infiltrated by lymphocytes and large mononuclear cells. The patient was living and well fifteen and one-half years after operation.

CASE 4. The lesion was an incidental finding in an adenomatous goiter, the clinical data concerning which were not available. There was a small scirrhous, subcapsular mass which was not encapsulated but was sharply differentiated. This mass resembled the lesions described in Cases 1, 2 and 3 and was about 1 cm. in its maximum diameter. It manifested greater degenerative changes with desquamation of degenerate acinar epithelial cells and compression of the atypical acini by the actively proliferating fibrous connective tissue.

In these four cases the lesion of the thyroid corresponded to that described by Graham as "adenocarcinoma not arising in an adenoma." The diagnosis of "papilliferous carcinoid" is not intended to imply that all such lesions are papilliferous, or that there is no

TABLE I

Differential characteristics	Papilliferous cystadenoma	Papilliferous cystadenocarcinoma	Papilliferous adenoma	Papilliferous malignant adenoma	Papilliferous carcinoid
Origin	10 in thyroid gland 17 in aberrant thyroid tissue	20 in thyroid gland 15 in aberrant thyroid	15 in thyroid gland 2 in aberrant thyroid tissue	16 in thyroid gland 3 in aberrant thyroid tissue	4 in thyroid gland
Pathogenesis	Hyperplasia of lining of a cystic adenoma	Malignant change in a papilliferous cystadenoma	Intra-acinar epithelial hyperplasia in a follicular adenoma	Intra-acinar hyperplasia in a malignant adenoma	Focal hyperplasia in non-tumorous thyroid gland
Gross structure	Cystic	Cystic	Solid	Solid	Solid scirrhous and small. Not encapsulated
Acini	Secondary differentiation of papilliferous epithelium	Secondary differentiation of papilliferous epithelium	Primary structural unit of tumor	Primary structural unit of tumor	Atypical
Papillae	Coarse, arborescent, macroscopic, and seat of degeneration	Coarse, arborescent, macroscopic, and seat of degeneration	Delicate and simple or complex and usually microscopic	Delicate and simple or complex and usually microscopic	Microscopic and simple
Secondary changes	Fibrosis, lymphocytic infiltration, old and recent hemorrhage, calcification	Fibrosis, lymphocytic infiltration, old and recent hemorrhage, calcification			Fibrosis, lymphocytic infiltration
Malignancy	None	Capsular invasion metastasis to regional lymph nodes	None	Blood vascular invasion, metastasis to regional lymph nodes, capsular invasion	None

such tumor of the thyroid as an adenocarcinoma not arising in an adenoma. These lesions simulated tumor because of the sharp distinction between their cells and structure and those of the surrounding thyroid gland (Fig. 4). The size, shape and staining qualities of the epithelial cells, the shape of acini, the character of the papilliferous hyperplasia, the amount and disposition of stroma and the sharp delimitations of the lesions differentiated them from the usual manifestations of hypo- or hyperinvolution in glands, the seat of secondary hyperplasia. They more nearly resembled malignant than benign tumors, because of the absence of encapsulation and the apparent invasion of a densely fibrous stroma which was continuous with the interstitial tissue of the surrounding gland.

There were several reasons for considering these lesions nontumorous. The absence of a capsule militated against the probability of benign tumor. Their small size, their failure to invade adjacent tissue and the non-existence, in a collection of over 130 malignant tumors of the thyroid, of a type of tumor which had apparently evolved from such a lesion, argued against a malignant tumor and led us to consider other pathogenetic possibilities. All four of the lesions studied were small, subcapsular and situated in glands altered by abnormal involution. In thyroids the seat of pathological involution, any and all of the features characterizing the lesions described *may* occur, and the fact that all of these changes occurred in a single isolated area was unusual but did not of necessity indicate neoplasia.

Summary

1. One hundred and two papilliferous tumors of the thyroid or of aberrant thyroid tissue were studied and classified. Twenty-eight of these were from the Institute of Pathology of Western Reserve University and seventy-four were published case reports from other sources.

2. The differential characteristics of the various types are tabulated in Table I. As indicated in the discussion of the various types of tumors these characteristics were not invariably present, but represented the features that were most common.

3. The papilliferous character of adenomas and malignant adenomas did not distinguish them from the non-papilliferous forms of those tumors so far as growth was concerned, while the papilliferous

cystadenomas and cystadenocarcinomas constituted a group of tumors having peculiar and characteristic growth. The term "papilliferous" as applied to tumors of the thyroid is significant only in connection with papilliferous cystadenomas and papilliferous cystadenocarcinomas.

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DESCRIPTION OF PLATES

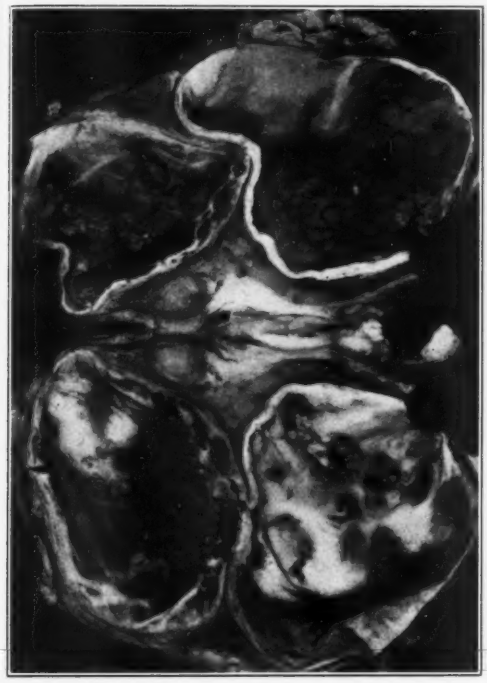
PLATE 151

FIG. 1. Papilliferous cystadenoma of left lateral aberrant thyroid tissue. Actual size.

FIG. 2. Dense hyalinized capsule of a papilliferous cystadenocarcinoma. Capsule is invaded by atypical follicles in which intrafollicular papilliferous hyperplasia of epithelium is seen. × 10.

FIG. 3. Portion of a papilliferous cystadenoma of lateral aberrant thyroid tissue in which original follicular structure of adenoma is not entirely replaced. × 240.

FIG. 4. Upper pole of one lobe of thyroid including capsule and small subcapsular papilliferous carcinoid. There is diffuse lymphocytic infiltration and proliferation of fibrous connective tissue in and around the lesion. × 30.



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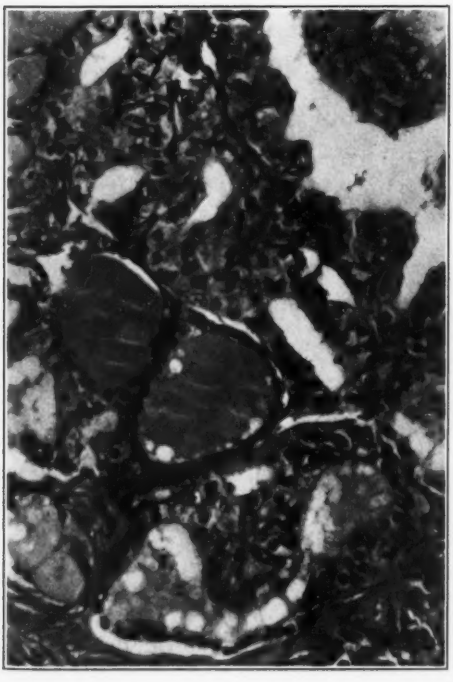

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4

Moritz and Bayless

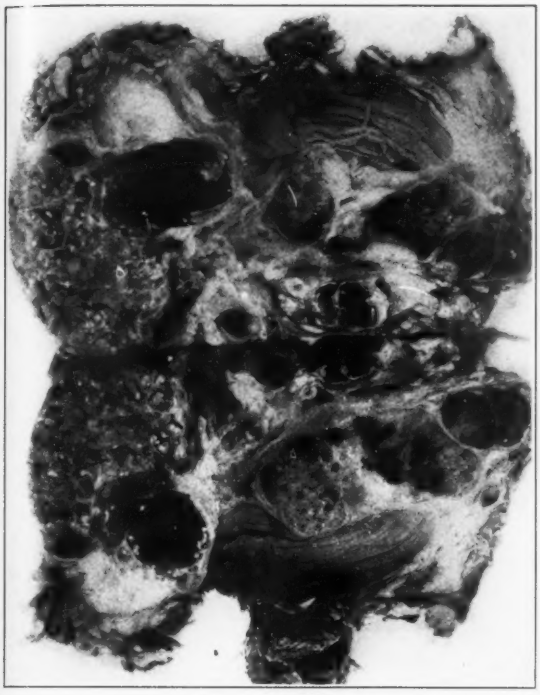
Papilliferous Tumors of Thyroid Gland

PLATE 152

FIG. 5. Papilliferous cystadenocarcinoma of right lateral cervical aberrant thyroid gland tissue. Three-fourths actual size.

FIG. 6. Delicate arborescent papillae in a malignant adenoma. × 200.

FIG. 7. Invasion of tissue adjacent to a papilliferous cystadenocarcinoma of lateral aberrant thyroid tissue by atypical follicles lined by pleomorphic epithelial cells which exhibit papilliferous intra-acinar proliferation. Fibrosis and lymphocytic infiltration are marked. × 220.



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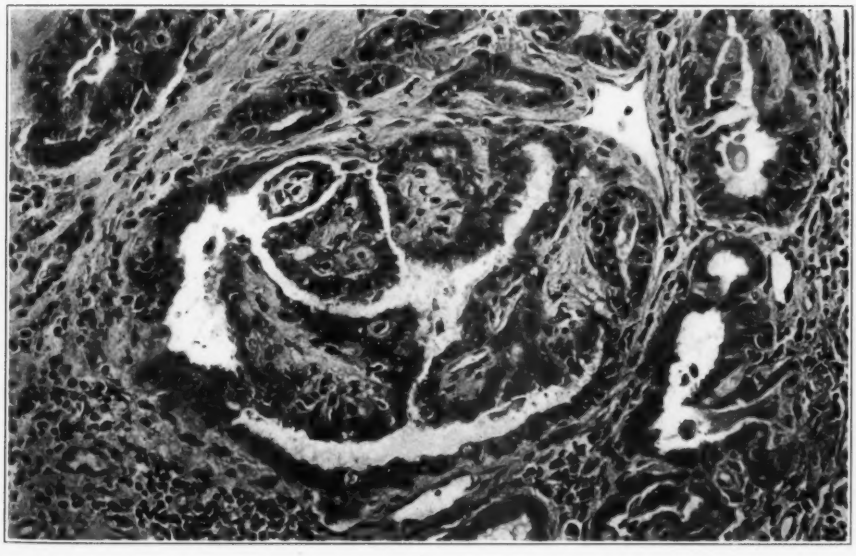

7

Moritz and Bayless Papilliferous Tumors of Thyroid Gland

A CASE OF MYELOMA WITH UNUSUAL AMYLOID DEPOSITION *

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A case of multiple myeloma with deposition of amyloid in the intestine and muscles of the thorax and left shoulder, together with a large "amyloid tumor" of the left shoulder joint, was reported in 1910 by Hueter.[1] In this instance no amyloid was found in its usual sites of deposition, namely the spleen, liver and kidneys. In reviewing the literature Hueter found only one other case of myeloma associated with amyloidosis (that of Askanazy in 1904) in which amyloid was present in the intestine. In 1916 Glaus [2] published a report of a case of myeloma in which amyloid degeneration was widespread, affecting the intestinal tract, mesenteric vessels, heart and striated muscles of the tongue and thorax. In addition, the substance was distributed in the blood vessels of the thyroid, pancreas, testes, liver, spleen, kidneys, adrenals and lymph glands. Calcium was present in some of the amyloid-containing areas.

Within the past few months Lubarsch,[3] Larsen [4] and Warren [5] have reported instances of amyloidosis of the cardiac, smooth and striated muscles, and in their papers have included brief abstracts of work previously published concerning amyloidosis of the muscular systems.

CASE REPORT

Clinical History: C. P., age 38 years, male, mulatto (History No. 222791, Necropsy No. 10389) was admitted to the Presbyterian Hospital September 16, 1929.

Chief Complaint: Pains in the muscles, joints and bones over entire body for nine months.

Past History: Typhoid fever twenty-two years ago. Jaundice nineteen years ago. Amputation of right leg above the knee fifteen years ago because of elephantiasis.

Present Illness: Severe cramp-like pains began first in the thigh and leg muscles, followed a month later by pains in the wrists, hands, fingers and knee. Associated with these were stiffness and numbness of the left hand and fingers,

* Received for publication June 1, 1931.

and stiffness of the left knee and hip. There was a gradual loss of strength and a loss of 25 to 30 pounds in weight during the last two or three months, although his appetite was greater than usual. He had polydipsia and some polyuria, the urine being either pale or milky in appearance.

Physical Examination: The patient was a chronically ill mulatto. The tongue showed a diffuse papillary atrophy, and the submaxillary lymph glands were enlarged. The heart was slightly enlarged to left and right, with a systolic whiff at the apex, a systolic blow in the mitral area and a systolic apical thrill. Blood pressure 120 systolic, 75 diastolic. The lungs were clear. In the abdominal wall was a firm, non-tender movable mass, approximately 10 by 6 by 6 cm. in size, lying in the oblique muscle group of the left flank. The spleen and kidneys were not palpable. The lower border of the liver lay 3 cm. below the right costal margin. The prostate was small and soft. The right leg had been amputated at the level of the midthigh. There was an atrophy of the interscapular and erector spinae muscle groups, left deltoid, biceps and triceps, left pectoral, thenar and hypothenar groups, and the muscles of the left calf. The right deltoid, muscles of the forearms, and right pectoral appeared hypertrophied. In the left thigh a large mass was present in the abductor muscle group. On the medial aspect of the right thigh was a smaller mass.

A neurological examination reported: "Coördination, deep and superficial reflexes, sensation and cranial nerves show no impairment indicative of any localizable pathology in the central or peripheral nervous system."

Temperature 99.2 F; pulse 80; respirations 20.

Laboratory Findings: Hemoglobin 50 per cent; red blood cells 3,010,000; white blood cells 8,700; polymorphonuclear leucocytes 66 per cent; lymphocytes 26 per cent; basophiles 1 per cent; large mononuclear leucocytes 7 per cent. Blood urea 0.54 gm. per liter. Blood Wassermann negative. Urine: specific gravity 1.009–1.020; albumin, heavy trace; occasional red and white blood cells and granular and hyaline casts; Bence-Jones protein present. X-ray films (No. 59338) of the skeleton showed diffuse rarefaction and small areas of bone destruction in the cervical, dorsal and lumbar vertebrae, ribs, clavicles, humeri, femora, pelvis bones and skull. No spontaneous fractures were visible.

Course of Illness: During the patient's stay in the hospital the mass in the left thigh grew larger, his shoulders increased markedly in size and a small mass appeared in the left antecubital fossa. The Bence-Jones protein disappeared from the urine, only to reappear during the three weeks before death. Edema of both elbows, left lower extremity and sacral region developed and anemia increased, the hemoglobin on January 20 being 29 per cent, red blood cells numbering 1,660,000 and white cells 2,250, with 74 per cent polymorphonuclear leucocytes. Biopsy specimens (Surgical Pathology No. 41510, Medical Pathology No. 2054) from the left thigh and right shoulder failed to show any tumor growth. The day before death the blood pressure had fallen to 60 systolic, 40 diastolic, respirations became slow and shallow and the pulse rapid. He grew irrational, became semicomatose and died February 1, 1930, four and one-half months after admission to the hospital.

Clinical Diagnosis: Myeloma, leucosarcoma (?), chronic nephritis, secondary anemia.

Autopsy Findings

The body is that of a markedly emaciated mulatto male with enormous shoulders in which masses are palpable. These are firm, non-movable and not sharply circumscribed. The mass in the right shoulder measures approximately 10 by 8 cm. In the left flank, filling the space between the crest of the ilium and the left costal margin, is another firm mass. On the lateral surface of the left thigh is a firm, non-movable swelling 15 cm. in length by 6 cm. in width. In the right groin, on the anteromedial aspect and immediately below Poupart's ligament, is a projecting, freely movable, oval mass 8 by 8 cm. in size, over which the skin is thick and nodular. Smaller firm masses are palpable in both antecubital fossae. Both arms are emaciated and the muscles seem small. The hands are edematous. The right leg has been amputated above the knee and the muscles of the stump are atrophied.

The peritoneal cavity contains about 75 cc. of slightly milky fluid. The left pleural cavity contains 1,000 cc. of clear, yellow fluid and the right contains 1,300 cc.

Dissection of the shoulders shows similar changes in each. The skin is not unduly adherent to the underlying tumor-like structures and there is a layer of voluntary muscle covering each mass. Section through the deltoid muscles shows that immediately beneath a thin superficial layer of muscle the entire region is occupied by a firm, lardaceous substance 3 to 4.5 cm. thick, which surrounds the shoulder joints and the heads of the humeri, extending down over them to the level of the surgical necks. These masses have invaded or replaced the regional structures so that the normal landmarks are no longer seen. On the cut surface of the "tumor" delicate and coarse bands of connective tissue separate masses of homogeneous, white, translucent material. Between the coarser bands of connective tissue are narrow clefts and spaces. The tumor-like mass extends down to the periosteum from which it can be separated easily. On opening both shoulder joints the articular surfaces appear smooth. From the glenoid fossa of the right joint a small amount of smooth, firm material, suggesting pale fat, is removed. On section of the head of the right humerus the cut surface is grayish yellow, mottled with small, white, soft masses which vary in size from 3 to 5 mm.

At the right sternoclavicular joint the bones are firmly bound together by dense white tissue. On section the sternal portion of the right clavicle and the attached segment of the manubrium contain in their marrow cavity firm grayish masses, that in the clavicle measuring about 3 cm. in length, while the remainder of the cavity contains only slightly reddish fat. The lower ends of the cervical muscles attached in the region of the right sternoclavicular joint are pale.

The mass in the left flank lies in the oblique muscles of the anterolateral abdominal wall, extending medially to the lateral border of the left rectus muscle, and it fills the space between the iliac crest and the lower costal margin. The skin over this mass is not unusually adherent to it and there is no extension of the tumor-like growth through the underlying parietal peritoneum. The mass is easily removed from the crest of the ilium, leaving no perceptible irregularity of the innominate bone in the region of attachment. After removal the mass measures roughly 15 by 10 by 6 cm. On its external surface is a thin layer of striated muscle, below which is a zone 2.5 to 3 cm. thick similar in appearance to the lardaceous substance about the shoulder joints. Internal to this is a layer of pale muscle fibers stippled with hemorrhages, but many fibers appear to be replaced or widely separated by the firm white substance. Internal to this band is still another layer of white homogeneous material 1 cm. thick, with a few pale muscle fibers scattered through it.

A section from the swelling on the left thigh is similar in appearance to the masses about the shoulders. The mass on the anteromedial aspect of the right thigh lies in the subcutaneous fat. Its cut surface is pearly white and firm.

Sections from the tumor-like masses, treated with iodine, turn a mahogany brown color.

The ribs are free from nodular enlargements or fractures. Section through one discloses a pale brownish red fatty marrow. The bodies of the second, third and fourth lumbar vertebrae are mottled by irregular, whitish, soft masses varying in size up to 1 cm.

The heart is essentially normal. The aorta presents a mild degree of atheroma. The lungs show partial atelectasis of their lower lobes. Thyroid normal.

The spleen weighs 220 gm. The capsule is slightly thickened, the pulp reddish brown and not unusual.

On the anterior surface of the right lobe of the liver are fibrous adhesions. The organ weighs 1660 gm. and through the capsule appears pale brownish red in color. On section the lobular markings are small and poorly defined, and scattered over the cut surface are numerous yellow flecks 1 to 2 mm. in diameter.

The gall-bladder contains one mulberry stone.

The adrenals are of normal size but slightly firmer in consistence than usual. On section there is some pallor of their cortices.

The left kidney measures 10 by 5.5 cm. and the right 9 by 5.5 cm., each being slightly smaller than normal. The capsules strip easily. Scattered over the surfaces are numerous, slightly raised, gray elevations 1 to 2 mm. wide, which in places have become confluent. The remainder of the surface is deep reddish brown and a few cysts 1 to 4 mm. in diameter are present. On section the normal renal markings are obscured. The cortices are narrow and throughout them are innumerable grayish areas 0.5 to 2 mm. in size, while in some regions the entire cortex is gray. The pyramids are pale and streaked with red linear markings.

The bladder is distended with urine containing white flocculent masses. The bladder wall is slightly trabeculated and the mucosal surface is free from exudate.

The testes are small and their cut surfaces darker brown than normal. The prostate is small. The seminal vesicles are normal. The gastro-intestinal tract is normal save for melanosis of the cecum and ascending colon.

Microscopic Findings

Bone Marrow from Sternum, Ribs and Vertebrae: Masses of cells having the morphology of plasma cells are present and among them are many with two or more nuclei. About the capillaries these cells form a single palisade-like layer. About the tumor cells is a stroma of moderately dense connective tissue in which are many delicate collagen fibrils. Large blood vessels are not numerous but in the walls of some amyloid is demonstrated with methyl violet.

Rib: The muscle fibers and adipose tissue attached to the external surface show extensive amyloid changes similar to those to be described below.

Masses about Shoulders and in the Striated Muscles: In places many normal muscle fibers remain, but there are also many which

are necrotic, vacuolated or atrophic. Others show waxy degeneration. The sarcolemma nuclei of occasional necrotic individual fibers have proliferated, forming large nuclear masses at the ends of the fibers. Between the muscle cells are trabeculae of amyloid, giving characteristic staining reactions with Congo red and methyl violet. Between longitudinally cut fibers these amyloid strands run parallel to the long axes of the fibers, while in those cut transversely amyloid forms a delicate anastomosing network between adjacent fibers, often appearing between them in two delicate bands, as if deposited beneath the endothelium of the capillaries. No amyloid is found in the muscle cells themselves. In regions where the amyloid deposition is more abundant the muscle fibers are widely separated by small and heavy strands and irregular masses of amyloid. In many regions no muscle fibers are present, but the entire mass is composed of amyloid arranged in masses or clumps or in delicate or coarse anastomosing bands, the whole presenting a reticular or "porous" structure. Moderate numbers of capillaries and thin-walled blood vessels are present, and elongate nuclei suggesting morphologically those of connective tissue cells are scattered through the amyloid-containing areas. A few multinucleated giant cells, some of them partially surrounding amyloid particles, occur. In some of the sections are islands of adipose tissue.

Mass from the Right Glenoid Fossa: The mass is composed mainly of amyloid, together with a small amount of dense connective tissue in which are many blood vessels.

Heart: Amyloid has been deposited in the walls of both arteries and veins, forming in places heavy masses which markedly narrow the lumina. It also surrounds many of the cardiac fibers, appearing about individual fibers as a thin mantle. In some instances it has been deposited in the fibers themselves and it appears in small masses beneath the endocardium. In one area there has been widespread necrosis of the cardiac fibers with an infiltration of polymorphonuclear leucocytes about them.

Aorta: In the middle third of the media is a fine deposit of calcium.

Spleen: Amyloid occurs in the walls of the central arterioles and about some of the capillaries. In the malpighian bodies it forms irregular anastomosing masses and strands.

Liver: Amyloid deposition is heavy in the walls of the arteries of

the portal spaces and in those arteries adjacent to the capsule. Smaller deposits of it appear in the walls of some of the veins. None is seen about the sinusoids.

Pancreas: Amyloid occurs both in the arteries and veins of the interlobular septa and in the arterioles of some of the lobules. At the periphery of a few of the pancreatic lobules delicate, anastomosing fibrils of the substance surround a few of the acini. In the peripancreatic adipose tissue the fat cells are surrounded by thin mantles of amyloid and the larger blood vessels contain a subendothelial deposit.

Adrenal: Practically the entire fascicular zone is replaced by amyloid and it is also seen in the vessel walls in the surrounding fat.

Kidney: Amyloid is abundant in the capillary tufts of many of the glomeruli and is widely distributed throughout the arterioles and capillaries in other parts of the kidney. Less commonly it appears in the basement membrane of the tubules. Practically all the glomeruli have undergone sclerotic changes, many of them being reduced to small hyaline scars. The tubules are either atrophic or are dilated and filled with casts, about some of which lie giant cells. Calcium is also present in some of the tubular lumina. The interstitial tissue of the cortex is condensed in many places and is infiltrated with lymphocytes and plasma cells. About the capillaries and medium-sized arteries in the peripelvic fat amyloid is abundant.

Testis: Spermatogenesis is not in evidence, many of the cells in the tubules being those of the Sertoli type. In the blood vessels in the interstitial tissue and in the membrana propria of many of the tubules amyloid is present. It occurs also in the walls of the blood vessels supplying the tunica albuginea.

Seminal Vesicles: No amyloid found.

Prostate: Amyloid has infiltrated not only the walls of the blood vessels, but it appears beneath the epithelium of the prostatic glands, in places filling the interglandular stroma with coarse parallel or anastomosing fibrils. It occurs also in groups of fibers in many of the smooth muscle bundles in the gland, and it surrounds the capillaries traversing several periprostatic sympathetic ganglia.

Stomach and Duodenum: The section includes the pyloric end of the stomach and the adjoining part of the duodenum. Methyl violet demonstrates amyloid about the capillaries and in the stroma of the gastric and duodenal mucosa where it partially or completely

surrounds many of the glands. About Brunner's glands the deposition is heavy and the amyloid forms wide trabeculae. It is present in the muscularis mucosae and in all the muscular coats of both stomach and intestine groups of muscle cells appear rose red in methyl violet preparations. Amyloid occurs also in the walls of the blood vessels in all the layers.

Colon: Amyloid is found only in the walls of the blood vessels of the submucosa and subserosa.

Anatomical Diagnoses: Multiple myeloma; amyloidosis of heart, spleen, liver, pancreas, adrenals, kidneys, testes, prostate, stomach, intestine, bone marrow, adipose tissue, sympathetic ganglia, shoulder joints and muscles of neck, shoulders, thorax, abdominal wall and thighs; infarct of heart; hydrothorax, bilateral; atelectasis of lungs, bilateral; cholelithiasis, calculus in gall-bladder; medial calcification of aorta; melanosis of colon; fibrous peritoneal adhesions.

Comment

The case is one of generalized amyloidosis, associated with a widespread myeloma which involves, according to the pathological and X-ray findings, the spine, ribs, clavicles, humeri, femora, pelvic bones and skull. Microscopic examination shows the myeloma to be of the plasma cell type, in which the cells lie in a well developed fibrillar stroma. Of special interest are the sites of amyloid deposition with the formation of "amyloid tumors" about the shoulder joints and in the striated muscles of the abdominal wall and thighs. Undoubtedly the masses palpable in both antecubital fossae were also amyloid in nature, though this fact was not established at autopsy. Of the organs usually showing amyloid degeneration, the spleen, kidneys and adrenals in this case are affected but the liver is spared, except for the deposition of the substance in the walls of the hepatic vessels. Amyloid is abundant, however, in organs and tissues less commonly involved in the degenerative process and it appears in considerable quantities in the heart, gastro-intestinal tract, prostate and adipose tissue. Smaller depositions of it are present about the blood vessels of the testes, the periprostatic ganglia, the bone marrow and pancreas, and in the last organ a few of the lobules are infiltrated by it.

The presence of amyloid in cases of myeloma in which the Bence-Jones protein is an accompanying feature affords ground for spec-

ulation as to the relationship which may exist between the two substances. In the present case the homogeneous, eosinophilic substance, so widely deposited throughout the organs and tissues, has given characteristic staining reactions with iodine, Congo red and methyl-violet and has been considered true amyloid. Because of the diversity of opinion regarding the exact chemical nature of the Bence-Jones protein and amyloid, and the unsettled question as to their origin, it is impossible to decide whether we have present two chemically different proteins or whether the amyloid-like substance may be considered a "consolidation of the Bence-Jones protein," a suggestion offered by Wells [6] in regard to the case of Glaus.

Summary

A case of multiple myeloma is reported with an associated extensive amyloidosis. Of interest, both clinically and pathologically, are the huge tumor-like masses which resulted from the deposition of amyloid in the striated muscles and about the shoulder joints. Worthy of note, also, is its presence in the spleen, kidneys, adrenals, gastro-intestinal tract, heart, pancreas, reproductive organs, sympathetic ganglia and adipose tissue and its absence from the parenchyma of the liver.

Note: I am indebted to Dr. W. W. Palmer for permission to transcribe the clinical records and to Mr. Alfred Feinberg for the drawings.

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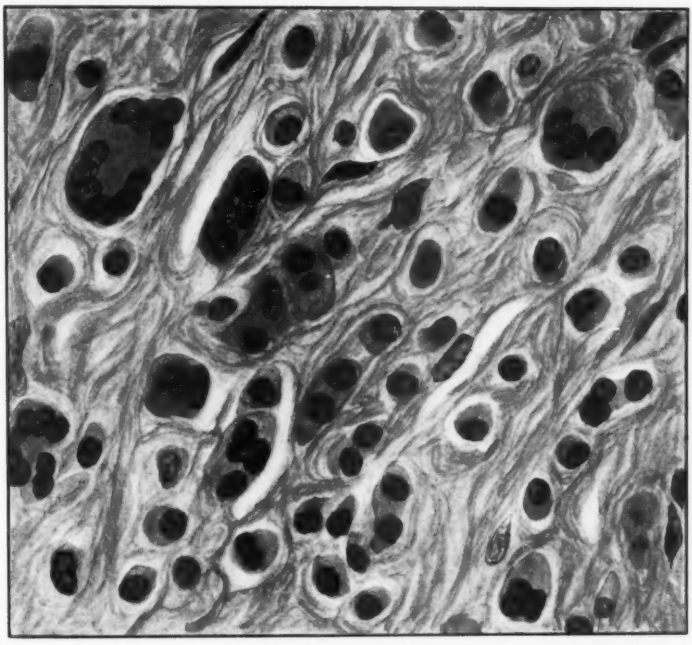
DESCRIPTION OF PLATE

PLATE 153

FIG. 1. Plasma cell myeloma.

FIG. 2. Amyloid deposition in striated muscle.



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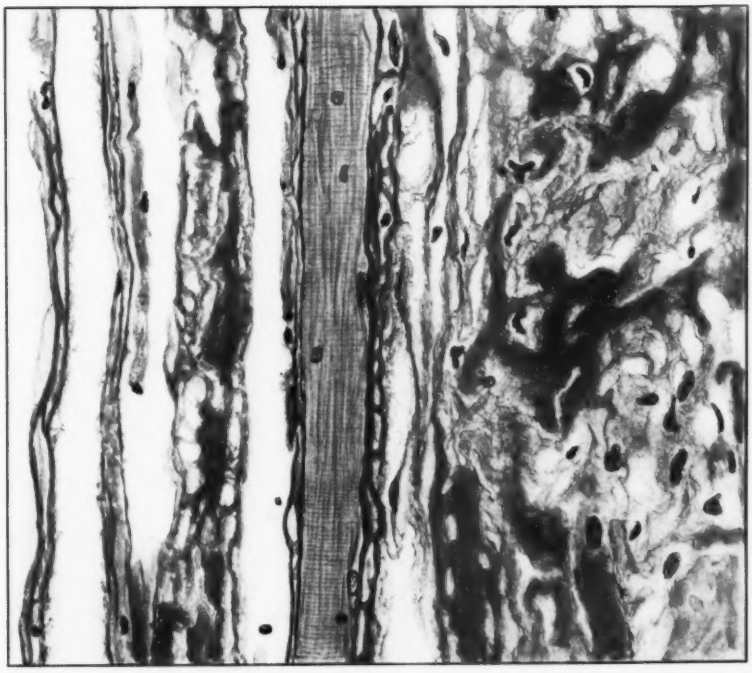

2

Paige Myeloma with Amyloid Deposition

MELANOSIS MUCOSAE APPENDICIS VERMIFORMIS *

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Review of Literature

Melanosis of the appendiceal mucosa has been studied hitherto only in connection with melanosis coli. The purpose of the present paper is to show the frequency of this condition in surgically removed appendices and to attempt to analyze its relation to other available data. Little has been added to the pathological anatomy and histology of melanosis coli since the thorough description of this condition by Pick [1] in 1911, who collected twelve cases from the literature, (one of Virchow's, one of C. J. Williams', one of G. N. Pitt's, one of Rolleston's, one reported by Grawitz, seven by Solger) and reported six additional cases, two of which were autopsied by Orth and one by Fraenkel.

Pick described granular brown pigment usually intracellular in round, oval, angular or irregularly shaped mononuclear cells about 14 microns in diameter, limited strictly to the mucosa and to the colon. Pigmentation was reported in the mucosa of the appendix in three of his own cases, in one of which there was distal obliteration. The earlier literature did not mention the appendix. He considered the pigment a melanin, and in 1930 with Brahn [2] reported further chemical examinations of pigment isolated from the melanotic mucosa which show that the pigment is a true melanin.

Simon [3] examined 77 appendices, 43 removed surgically and 34 at autopsy, finding pigment in the mucosa in 14. From his protocols this pigment appears to have been iron-free, intracellular in enlarged connective tissue or chromatophore-like cells situated in the interglandular stroma of the mucosa, and occasionally in the lymph follicles. He also cited four cases of "nodular and villous melanosis of the colon" in which the pigment contained iron, and hence were probably not true melanosis. Schmidt [4] examined 20 appendices removed at autopsy and found "hemosiderin" pigment in 15, but noted no melanin. Whether the methods used were adequate to

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distinguish these pigments is uncertain. Huecke [5] confined his discussion largely to the nature of the pigment of melanosis coli, finding it free from heavy metals, acid insoluble, bleached by peroxides, tinged blue by Nile blue after bleaching, and stained brown by silver nitrate. He considered it more closely related to the lipofuscins than to the true melanins. The pigment was contained in both fixed tissue and wandering cells.

Henschen and Bergstrand [6] analyzed 225 autopsies as to the presence, histological distribution, age and sex distribution, and relation to other factors of melanosis coli. In 5 of these 225 cases melanosis was definitely recognized grossly, and was found histologically in 65, or about 29 per cent. They found pigment also in the ileum and once in the mesocolic lymph glands. The appendix was missing in 3 cases, obliterated and pigment-free in 12 cases, pigmented alone in 10 cases, pigmented in association with colonic pigmentation in 25 cases, and unpigmented in the presence of cecal pigment in 15 of the 65 cases showing pigment in some part of the intestinal mucosa. In how many of the pigment-free cases the appendix was absent or obliterated is not stated. They found an association of melanosis with chronic constipation, and an increased prevalence in the higher age groups (35 of 85 cases over 60 years of age). The instances of isolated appendiceal melanosis were all in patent, dilated appendices.

Microchemical examinations showed that the pigment resembled that in the chorioid coat of the eye in many respects, but differed in others. They found the pigment in mononuclear cells about 15 microns in diameter which they considered as of macrophage type. The granules were at first small, later enlarging. Nuclear degeneration was noted, and instances of cells with much coarsely granular pigment and well preserved nuclei were interpreted as examples of secondary phagocytosis.

Niklas [7] reported two cases of colonic melanosis with intracellular and free crystalloid melanin-like pigment also in the mesocolic lymph glands. In one of these the appendix showed a wide-open lumen and a pigmented mucosa.

Bland-Sutton [8] observed melanosis of the mucosa in a surgical specimen removed for an annular carcinoma of the "iliac" colon.

McFarland [9] described melanosis coli similar to that described by Pick, and Henschen and Bergstrand. The pigment-carrying cells he

believed to be plasma cells which ranged from 7 to 20 microns in size. In 206 specimens of intestinal tissue there were 12 in which the colon was resected or examined in part in cases of chronic intestinal stasis. Eleven of these last were pigmented. Pigmentation of the appendix was noted specifically only in his Case 2.

In the discussion of McFarland's presentation, Ewing [10] stated that he encountered pigmentation of the large intestine somewhat frequently and believed that a lesser degree of this condition was not so infrequent as the literature would indicate.

Lignac [11] found 7 cases in 600 autopsies and observed one other at laparotomy. The pigmentation was confined to the mucosa and mesocolic lymph glands, and was more intense in the cecum and rectum than in the colon or appendix. The microchemical reactions were those of melanin, except that only a brown coloration was produced by 1 per cent silver nitrate.

Dalldorf [12] reported 5 cases of melanosis coli. The pigment was bleached more slowly by antiformin than was that of the liver or heart, and was contained both in fixed and wandering cells. Attempts to produce melanosis coli in a dog experimentally were unsuccessful, but the experiment lasted only eleven weeks.

Lubarsch and Borchardt [13] noted 17 cases of melanosis coli in some 5,000 autopsies. The cases occurred chiefly in the older age groups. In 100 appendices they found only three examples, 16, 25, and 33 years of age, all with chronic appendicitis.

Stewart and Hickman [14] reported the incidence of melanosis coli in 670 autopsies including 100 cases of carcinoma of the colon. In 600 autopsies, including 30 cases of carcinoma, gross pigmentation was present in 67 (11.2 per cent) with the same preponderance in the higher age groups as reported by Henschen and Bergstrand. The 100 cases of carcinoma of the colon showed a much higher incidence of melanosis, 55 cases on gross examination and 13 more microscopically. Extension of pigmentation into the appendix was noted in some cases of melanosis coli, and they stated that melanosis was not infrequent in surgically removed appendices.

Description and Analysis of Material

The material herein reported comprises 750 appendices examined in the course of the past three and a half years. As the condition apparently increased in frequency as greater familiarity with it was

acquired, fresh sections were prepared of all negative cases within the last three months of the work and reexamined. It was found that no significant variation in frequency had actually occurred.

TABLE I

Variation in Frequency of Melanosis in 750 Appendices

Count	*1st* 100	*2nd* 100	*3rd* 100	*4th* 100	*5th* 100	*6th* 100	*7th* 100	*last* 50	Total per cent
Per cent	35	35	32	44	51	25	31	26	35.5

The histological picture corresponds well with that described by Pick. The pigment is pale yellow to deep brown in color, finely to coarsely granular in form, insoluble after formalin fixation in alcohol, acetone, benzol, xylol, hydrochloric and sulphuric acids. It does not react for free iron by the ferrocyanide procedure. It tinges orange-red with safranin and blue-green to yellowish green with methylene blue or toluidin blue, and remains unstained by basic fuchsin. In view of the extensive investigation of the chemical nature of this pigment by various authors, further tests of its nature were not made, the above being deemed sufficient for its identification as a melanin.

This pigment is usually contained in cells which are generally confined strictly to the stroma of the mucosa, only rarely being found in the periphery of the lymph follicles. The cells are large and round with broad cytoplasm, or stellate, fusiform or angular with narrower cytoplasm, but without the long slender processes seen in the chromatophores of the iris. The nuclei of both types, where distinguishable, are round or oval, leptochromatic in structure, with narrow nuclear membrane, small nucleoli and small chromatin granules.

In several cases there was an accumulation of large round mononuclear cells with leptochromatic vesicular nuclei just beneath the surface epithelium between the mouths of the glands. These cells contained many fine acid-insoluble granules which were not visibly colored and which stained pale blue with toluidin after two hours' extraction with 20 per cent sulphuric acid. As such cases often contain typical pigment in the deeper layers of the mucosa these granules are regarded as prophases of typical melanin.

For the purposes of correlation with various other factors of different grades of pigmentation the cases have been arbitrarily divided

into five classes: (1) negative; (2) those showing only occasional pigment-laden cells in one or more cross-sections, designated as +; (3) those showing a few pigment cells as ++; (4) a moderate number as +++, and (5) those with heavy pigmentation which is often macroscopically evident as ++++. The rating was done on paraffin sections extracted first with 20 per cent sulphuric acid and then stained thirty seconds in 0.1 per cent toluidin blue. This method brings out the pigment quite conspicuously as green granules, and was selected for the survey of a large number of specimens as giving more histological detail than unstained sections, and also as applying two of the reactions for melanin.

The distribution according to age shows a slight increase in average age as the intensity of pigmentation increases (Table II).

TABLE II

Age Distribution by Decades, and Average Ages in Various Grades of Melanosis

Grade	0–9	10–19	20–29	30–39	40–49	50–59	60–69	Age not given	Average age	Total No.
Negative. .	1	24	213	155	50	19	4	18	30.7	484
+	2	4	48	42	9	2	1	3	30.1	111
++	0	4	24	36	7	4	0	9	32.2	84
+++	0	2	16	21	9	3	0	3	32.8	54
++++...	0	1	2	9	3	0	0	2	34.2	17
Total	3	35	303	263	78	28	5	35	30.99	750

Adding those showing traces of pigmentation to those showing none forms a group showing about two years lower average age than those showing pigmentation rated at ++ or more (30.6 years against 32.6).

Grouping the cases according to race and sex is not especially valuable, as 665 of the total 750 are white males, corresponding to the predominance of this group among the beneficiaries of the Public Health Service. The incidence in this group is not significantly different from that in the entire series, and the groups of white females and of all non-white are so small that the somewhat greater percentage variations shown are not particularly significant (Table III).

Dividing the cases according to occupational groups showed no great differences in the five groups used except that the group com-

prising seamen, marine firemen and other subordinate seafaring personnel shows a somewhat lower total incidence of pigmentation than the other groups (Table IV), and the handworkers ashore a higher percentage.

TABLE III

Distribution of Melanosis by Sex and Race

Sex and race	Negative		+		++		+++		++++		Total No.
	No.	%	No.	%	No.	%	No.	%	No.	%	
White males....	425	63.9	103	15.5	75	11.3	48	7.2	14	2.1	665
White females..	26	76	3	9	2	6	2	6	1	3	34
All non-white...	27	67	4	10	4	10	3	5	2	3	40
Total *	484	64.5	111	14.8	84	11.2	54	7.2	17	2.3	750

* 11 cases in which race or sex and race were not stated are included in this group.

On grouping the cases according to concurrent histological diagnoses it is found that with acute inflammation or obliteration the incidence of pigmentation is markedly reduced, with subacute inflammation less so. For the purposes of this study acute appendicitis comprises those cases showing acute ulceration of the mucosa or diffuse polymorphonuclear infiltration of the outer parts of the appendiceal wall, hemorrhagic necrosis, or in a few cases localized polymorphonuclear infiltration of the mucosa. Subacute appendicitis comprises cases showing notable eosinophil and lymphoid cell infiltration in the outer layers, granulating ulcers in the mucosa, organizing exudates in the serosa and mesenteriolar fat, or pus-filled glands in the mucosa. Chronic appendicitis is taken to comprise appendices showing more or less scarring, atrophy or hyperplasia of lymph follicles, noteworthy eosinophilic infiltration in the mucosa, and adhesions or obliteration. Some appendices originally classed as "normal" were placed in this group, as it was found that appendices removed at operations for other conditions where no symptoms of appendicitis were noted were not to be distinguished from those removed in "interval" operations for chronic appendicitis in many cases.

Bearing in mind the association of melanosis coli with chronic constipation noted in the literature, it was thought that the presence of fibrous adhesions might influence the incidence of melanosis in the appendix by producing local stasis. Adhesions were reported by the

TABLE IV

Occupational Distribution of Melanosis

	Seafaring groups										"Shore" groups										No occupation or not stated = 56					Total 750				
	Officers, Petty officers = 82					Seamen, firemen, etc. = 370					Professional, clerical, etc. = 43					Laborers mechanics, housewives, hand workers, = 199															
	−	+	++	+++	++++	−	+	++	+++	++++	−	+	++	+++	++++	−	+	++	+++	++++	−	+	++	+++	++++	−	+	++	+++	++++
Number	52	13	6	9	2	251	54	35	24	6	26	9	4	4	0	122	25	32	13	7	33	10	7	4	2	484	111	84	54	17
Per cent	63	16	7	11	2	68	15	9	6	2	60	21	9	9	0	61	13	16	7	4	59	18	12	7	4	64	15	11	7	2
Per cent	79			21		82			18		81			19		74			26		77			23		78			22	

operating surgeons in 158 cases, of which 29 were completely or partly obliterated. Three of these 29 and 10 others showed subacute appendicitis, and 5 showed acute appendicitis. The group classed as "chronic without obliteration" showed no appreciable influence of the presence of adhesions (Table VI).

TABLE V

Relation of Melanosis to Acute and Chronic Appendicitis

Grade	Acute		Subacute		Chronic without obliteration		Chronic distal ½ obliterated		Chronic distal ½ obliterated		Chronic complete obliteration		All appendices*	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Negative.....	130	91.5	79	71.8	220	51.9	17	59−	4	0	26	93−	484	64.5
+.....	6	4.2	16	14.5	82	19.3	4	14−	3	0	0	0	111	14.8
++.....	4	2.8	6	5.4	68	16.0	5	17+	1	0	0	0	84	11.2
+++.....	2	1.4	9	8.2	40	9.4	1	3+	1	0	1	4−	54	7.2
++++.....	0	0	0	0	14	3.3	2	7−	0	0	1	4−	17	2.3
Total	142		110		424		29		9		28		750*	

*8 appendices which are included in the totals do not appear elsewhere in this table, their diagnoses being tuberculosis in 4, carcinoid in 2, adenocarcinoma in 1 and autolysis in 1.

TABLE VI

Relation of Melanosis to Adhesions and to Lymph Follicle Changes

Grade	All adhesions		Adhesions, chronic without obliteration		Hyperplasia of lymph follicles		Partial atrophy, partial hyperplasia		Atrophy of lymph follicles	
	No.	%	No.	%	No.	%	No.	%	No.	%
Negative..	93	60.1	55	50.5	73	55.3	35	53.8	76	50.7
+.....	23	14.6	19	17.4	27	20.5	11	16.9	26	17.3
++.....	23	14.6	21	19.3	19	14.4	10	15.4	29	19.3
+++.....	15	9.5	11	10.1	10	7.6	8	12.3	14	9.3
++++...	4	2.5	3	2.8	3	2.2	1	1.5	5	3.3
Total	158		109		132		65		150	

The degree of atrophy or hypertrophy and hyperplasia of the lymph follicles showed little influence on the incidence of melanosis, there being possibly a slightly higher incidence of pigmentation in the group with atrophied follicles (Table VI). Only the group classed as "chronic without obliteration" was used in this last tabulation, in order to avoid the influence of obliteration and of subacute and acute inflammation already demonstrated.

The group of "chronic appendicitis without obliteration" was next analyzed as to the relation of the incidence of melanosis to the duration of symptoms of chronic appendicitis. The group designated "no symptoms" includes the appendices removed at herniotomies, pelvic operations, and at laparotomies for other causes in instances where there had been no symptoms attributed to the appendix. The group designated "0–6 days" includes the cases in which no specific duration of symptoms was given, but the case designated clinically as "acute appendicitis," while similarly diagnosed "subacute appendicitis" is included in the group 7–29 days. Cases diagnosed clinically as "chronic with unspecified duration," or "duration of years" are grouped with those of specified duration of over two years (Table VII).

TABLE VII

Relation of Duration of Symptoms of Appendicitis to the Incidence of Melanosis in the Chronic, Non-Obliterative Group

Grade	No symptoms		0–6 days		7–29 days		1–6 months		7 mos. –2 yrs.		2 years, chronic		Total of group	Average of specified duration		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		*yr.*	*mos.*	*days*
Negative	20	51	15	50	23	51	57	59	48	52	55	48	218	1	4	19
+	12	31	7	23	11	25	12	13	17	18	21	18	80	2	3	20
++	5	13	4	13	6	13	20	21	14	15	19	17	68	1	11	21
+++	2	5	4	13	3	7	4	4	10	11	14	12	37	2	1	16
++++	0	0	0	0	2	4	3	3	4	4	5	4	14	2	4	16
Total	39		30		45		96		93		114		417			

While the various symptom-duration groups shown in Table VII show no significant variation among each other or with the "no symptoms" group in the total percentage of positives, there seems to be a significant progressive increase in proportion of the grades of pigmentation greater than traces (+), and the average duration of symptoms of chronic appendicitis appears to be significantly greater in the pigmented cases than in the non-pigmented.

As Henschen and Bergstrand noted dilatation in melanotic appendices, and assigned "local constipation" as the cause of isolated appendiceal melanosis, it was considered desirable to correlate the degree and incidence of melanosis with the presence or absence of dilatation. Five hundred and ninety-five of the 750 appendices of the series were received fixed in an unopened state, and were considered suitable for the estimation of dilatation. This was esti-

mated on the usual cross-sections, dilatation of one, two or all of three sections being recorded. The results for all appendices appear in Table VIII, those for appendices without acute or subacute inflammation or obliteration in Table IX. On calculating percentage distribution of the different grades of melanosis between contracted and partially or completely dilated appendices, it appears that pigmentation is distinctly more frequent in the latter group (Table X).

TABLE VIII

Degree of Melanosis in Contracted and Dilated Appendices

Dilatation	–	+	++	+++	++++	Total
Lumen small	231	32	35	14	3	315
Dilated 1 level	63	28	14	7	1	113
" 2 levels	56	20	7	4	3	90
" 3 levels	37	10	10	13	7	77
Total	387	90	66	38	14	595

TABLE IX

Degree of Melanosis in Contracted and Dilated Appendices (Chronic Appendicitis Without Obliteration)

Dilatation	–	+	++	+++	++++	Total
Lumen small	96	17	27	9	2	151
Dilated 1 level	29	22	12	5	1	69
" 2 levels	29	15	6	4	2	56
" 3 levels	20	9	8	10	7	54
Total	174	63	53	28	12	330

TABLE X

Percentage Distribution of Varying Grades of Melanosis in Contracted and Dilated Appendices (Chronic Appendicitis Without Obliteration)

Degree of melanosis	Lumen small		Lumen dilated		Total No.
	No.	%	No.	%	
Negative	96	64	78	44	174
+	17	11	46	26	63
++	27	18	26	15	53
+++	9	6	19	11	28
++++	2	1	10	5	12
Total	151		179		330

Discussion and Conclusions

Melanosis of the appendix resembles essentially the melanosis coli described by Pick and others, and probably often forms a part of that condition. The pigment is probably formed first as fine uncolored granules in large mononuclear cells immediately beneath the surface epithelium. The pigment-carrying cells appear to be of macrophage and fibroblast types.

The average age of patients with pigmented appendices is slightly greater than with no pigment. No especially significant differences in incidence were found on segregation according to race, sex or occupation.

The great diminution in frequency of melanosis in acute and obliterative appendicitides, while undoubtedly due in part to mucosal destruction is probably not due entirely to that factor, as non-obliterative, non-ulcerative subacute appendicitis shows a similar though less marked decrease in incidence.

Adhesions have no noteworthy influence on the incidence of melanosis, atrophy of lymph follicles is possibly associated with a slight increase, and dilatation is quite definitely correlated with an increased frequency and probably higher grade of melanosis. The duration of symptoms of chronic appendicitis appears to be definitely greater in melanotic than in non-melanotic appendices.

It is noteworthy that the frequency of melanosis here reported is greater than in any published reports on melanosis coli, and the association with chronic appendicitis with dilatation and of longer than average duration may indicate that such chronic appendicitis provides favorable conditions for increased deposition of the pigment.

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MAST MYELOCYTE LEUKEMIA IN A CAT*

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Mast myelocyte leukemia has been reported in man by Lazarus,[1] Joachim,[2] Tomaszewski,[3] DiGuglielmo,[4] Vasaturo,[5] Sabrazès,[6] Massa and Marinoni,[7] and Tinti,[8] counting as such only cases showing mast cell percentages above 20 per cent. This subvariety of myelogenous leukemia was so named by Joachim, who saw two cases. Vasaturo refers also to a case of Hubertin's showing 23 per cent mast cells and to a case of Sabrazès in 1924, the original reports of which could not be found.

TABLE I

Reported Cases of Myelocyte Leukemia in Man

Author	Date	White corpuscles	Mast cell percentage
Lazarus	1901	..	47 later 3.7
Joachim	1906	189,000–168,800	53.6 " 34.9
Joachim	1906	237,000–117,000	56.4 " 83.3
Tomaszewski	1911	267,400–130,000	28 " 40
DiGuglielmo	1925	..	40 " 50
Vasaturo	1925	550,000	55
Sabrazès	1926	80,000	22
Massa and Marinoni	1926	138,100	30.9
Tinti	1926	120,000	35

Autopsy findings have been reported only in Joachim's second case which showed in brief:

Bilateral serosanguinous pleural exudate, with lesser and more purely serous pericardial and peritoneal fluid accumulations; moderate enlargement of mediastinal, retroperitoneal, omental, cervical and inguinal lymph glands, most marked in the last; enlargement of the spleen to 2100 gm. with gray-white subcapsular foci of necrosis, and gray-white strands of leukemic infiltration in the red pulp; enlargement of the liver to 5400 gm. with pale color, indistinct lobulation with gray-white peripheries; and red to light gray-red femoral bone marrow. Marrow smears from various locations showed predominance of mast cells. Histologically the liver showed

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periportal and interlobular leukemic infiltrations consisting chiefly of mast cells, but including also numbers of neutrophils, eosinophils and lymphocytes, and marked dilatation of the intralobular capillaries. These contained many highly vacuolated large mononuclear cells, red and white corupscles, with predominance of mast cells among the latter. Numerous mitoses were seen in the infiltrated areas, presumably in mast cells, the high degree of water solubility of the specific granulations when satisfactory nuclear stains were used rendering this uncertain. Necroses containing mast granules or nuclear débris, hemorrhages and irregularly distributed leukemic infiltrations were seen in the spleen; leukemic infiltrations occurred also in the renal cortex and in lymph glands.

Joachim was inclined to attribute the splenic necroses to the intensive roentgen ray therapy, and commented on the relatively smaller decrease of absolute numbers of circulating mast cells under X-ray treatment.

Leukemia in mammals was first reported by Leisering in 1858 (Folke Henschen [9]) in the horse. Cases have been reported since, most frequently in dogs, less often in horses, oxen, swine, mice, cats, rarely in goats and sheep, once in an elephant (Folke Henschen,[9] Hirschfeld,[10] Hutyra and Marek [11]), and have more often been of lymphatic type. In fact Jolly [12] stated that myelocythemia was unknown in the higher animals, except that certain older reports mentioned enormous splenomegaly and pyoid marrow, but without adequate blood examination. Hirschfeld, however, refers to cases of myelogenous leukemia in the dog (Lüdke in 1910), and in cattle (Knuth and Volkmann, Du Toit), and Julliard [13] stated that myelogenous leukemia was the more frequent form in animals.

In cats, reported cases of leukemia have been extremely rare. At the end of Siedamgrotzky's [14] detailed presentation of the first reported case of leukemia in the dog there is a four-line note: "Also in a cat which died of internal hemorrhage there was found a low grade leukaemia whose anatomical expression lay in a significant hyperplasia of the lymph glands and of the spleen (to twice normal size)." This case would appear to have been of lymphatic type. Nocard's report [15] refers to Siedamgrotzky's case and not to an original observation. In 1889 Sommer (Hutyra and Marek [11]) collected forty-six cases of leukemia in animals, among which were two in cats. DeDoës [16] reported a case of pseudoleukemia in a cat.

Lellmann's case [17] showed twelve red cells to one white in the peripheral blood, which with the given red cell count of 300,000 per cmm. would indicate a white count of about 25,000 per cmm. The white cells were chiefly "multinuclear" and some small mononuclears of the hyaline type and numerous "embryonal" stages of red corpuscles were present. The autopsy revealed an enlarged, firm, dark red spleen with prominent malpighian corpuscles, an enlarged, soft and friable, grayish yellow anemic liver with petechial subcapsular hemorrhages on the upper surface and indistinct lobular markings, enlarged (bean-size) soft grayish white lymph glands, dark red gelatinous marrow in the long bones and many small white subpleural nodules in the lungs. Lellmann's diagnosis of leukemia of mixed lymphatic, splenic and myelogenous form appears highly questionable, the findings suggesting rather a hyperregenerative, megaloblastic anemia.

In an annual report of animal autopsies Joest [18] includes the diagnosis of splenic leukemia in a cat. Ball [19] in a general paper on leukemias, noted the occurrence of myelogenous leukemia in the cat, but gave no case report or reference to the literature. Ball and Auger [20] diagnosed lymphatic leukemia in a cat dying after some months of progressive emaciation and loss of strength. The only gross postmortem finding was an enlarged (42 gm.) (normal 4 to 6 gm.) bluish red spleen with enlarged splenic corpuscles. Histologically there was hyperplasia of the lymphoid tissue of the enlarged malpighian corpuscles and hyperplasia of the reticular tissue of the hypertrophied pulp, but lymphocyte infiltration of the latter was not reported. Histological examination was apparently limited to the spleen. The blood showed "an intense anemia with considerable mononucleosis and inversion of the leucocytic formula." The reported data appear rather inadequate to establish the diagnosis.

Ball (Pinvidic [21]) considered leukemias as relatively frequent in dogs and cats, less frequent in horses, oxen, swine and birds, and said that they occurred in all forms in cats. Didier [22] (cited after Pinvidic) reported lymphatic leukemia in a cat, in which the liver was enlarged from the normal of 80 to 90 gm. to 480 gm., and histologically contained numerous lymphocytes in its capillaries and showed extensive areas of lymphoid infiltration. Pinvidic [21] diagnosed lymphatic leukemia at autopsy in a 5 year old cat. The spleen was enlarged to 38 gm., soft, bluish red in color, with tense capsule

and enlarged splenic corpuscles. The liver weighed 150 gm., was orange-red in color and flecked with yellowish necrotic foci a few millimeters in diameter. Lymph glands were not mentioned. Histological examination was apparently limited to the spleen. The splenic pulp contained numerous lymphocytes and small hemorrhages with marginal siderosis, the splenic corpuscles were enlarged, rather poorly defined and typically lymphoid in structure, and the blood in the veins contained numerous lymphocytes.

Lund [23] included two cats in a report of leukemia in thirty-four mammals (twenty-five lymphatic and nine myelogenous). One of the cats presented the lymphatic form, the other the myelogenous. General descriptions of the gross and minute pathology of each form were given, without case protocols. The lymphatic form was described as it occurred in swine. The myelogenous type presented marked splenomegaly, relatively slight lymphadenopathy, grayish or greenish yellow bone marrow and grossly evident leukemic infiltrations of liver and kidneys. Histologically there was generalized proliferation and dissemination of myeloid tissue which was composed chiefly of neutrophilic and eosinophilic myelocytes, myeloblasts, some normoblasts, megaloblasts and megakaryocytes.

Julliard [13] considered myeloid leukemia more frequent than lymphatic in animals, and noted its occurrence in the cat, but no specific case report was mentioned in Schmidt-Hoensdorf's review.[13]

Case Report

In our own case the animal was an apparently healthy cat weighing 2500 gm. which was being used in pharmacological studies by Dr. M. I. Smith of the National Institute of Health. The animal died unexpectedly about two hours after the intraperitoneal injection of paracresyl phosphate (2.5 gm. in 25 cc. olive oil) and was autopsied to ascertain whether death had been due to hemorrhage following the injection. Dr. Smith found the spleen enormously enlarged, filling the whole front and left side of the abdomen, measuring about 28 by 10 by 2 cm. or possibly 15 per cent less (Dr. Earle). From the estimated measurements I should place its weight between 200 and 300 gm. The spleen was soft, pale red in color with multiple grayish white areas up to 25 mm. in diameter, and foci suggesting suppurative necrosis were seen on the cut surface.

TABLE II

Occurrence of Leukemia in Cats

Author	Year	Form	Spleen	Lymph glands	Marrow	Blood	Remarks
Siedamgrotzky.....	1871	lymphatic?	twice normal	enlarged	..	..	..
Sommer	1889	..	..	..	..	..	collected 2 cases from literature
de Doës.....	1890	pseudoleukemia	..	..	..	normal?	..
Lellmann	1896	mixed	enlarged	enlarged	dark red	300,000 rbc 25,000 wbc	validity dubious
Joest	1905	splenic	..	..	..	..	no data
Ball	1912	myelogenous	..	..	..	..	no data
Ball and Auger	1924	lymphatic	42 gm.	not enlarged	..	anemia mononucleosis	validity not certain
Didier	1925	lymphatic	..	..	..	..	leukemic infiltration of liver
Pinvidic	1926	lymphatic	38 gm.	..	..	mobilization in veins	leukemic infiltration of spleen
Lund	1927	lymphatic	..	..	..	..	no specific data as to cats
Lund	1927	myelogenous neutrophil and eosinophil	enlarged	slightly enlarged	gray-yellow	..	no specific data as to cats
Lillie	1931	mast myelocytic	200–300 gm.	not enlarged	..	mobilization in veins	..

The liver was about twice normal size, its surface mottled by slightly raised patches 2 to 10 mm. in diameter, white to deep red in color.

The kidney was pale, its surface rough and irregularly lobulated, the cortex was pale and waxy in appearance, the medulla red.

The heart and lungs appeared normal. There was some pallor but no other gross abnormality of the intestines, omentum or mesentery. No enlarged lymph glands were noticed.

Blocks of liver, spleen and kidney were fixed in 10 per cent formalin, in Ringer's fluid, buffered to pH 7.6 by Dr. W. R. Earle of the Division of Pharmacology, and forwarded to the writer for histological examination.

Unfortunately the rarity of the condition was not realized at the time and no blood smears were taken, nor were the long bones opened. Hence our histological study is limited to the liver, spleen, and kidney and to such evidence of leucocyte increase in the blood as can be derived from sections of larger blood-filled vessels.

Histologically the spleen shows small malpighian corpuscles, and its pulp is packed with mononuclear cells containing numerous small metachromatically basophilic granules. The nuclei are often obscured, but where plainly visible are large, vesicular in form, with scanty chromatin and one or more medium-sized nucleoli.

When stained with Weigert's iron chloride hematoxylin and safranin the granules are quite small, metachromatically orange-red and discrete, and the nuclei are regularly plainly shown, black in color, round or oval in form, vesicular with chromatin condensation about the periphery, and scanty, very fine chromatin granules in some nuclei, coarser, more plentiful chromatin blocks in others. In the former type large round gray-stained centrally placed nucleoli are regularly seen, while in the more pachychromatic nuclei nucleoli are less conspicuous or not distinguished from the nuclear chromatin. The leptochromatic type predominates in the spleen and in the liver nodules, being somewhat less preponderant in the liver sinusoids. An occasional mast metamyelocyte with elongate bean-shaped nucleus is seen in the latter location.

The liver sinusoids are dilated and blood-filled. In them are numerous single mononuclear basophil granulocytes, many large myelocyte clumps in the sinusoids, and nodules composed of mast myelocytes and few non-granular myeloblasts in the portal connective tissues.

Scattered mast myelocytes are seen in the blood in the lumina of large veins in both the liver and kidney, and in a postmortem extravasation of blood into the renal pelvis.

The other renal changes present are apparently independent of the leukemic process, consisting of severe diffuse degeneration of the cortical tubules, numerous hyaline casts in the tubules of the hyperemic pyramid, occasionally periglomerular, and rarely intraglomerular fibrosis and areas of cortical interstitial lymphocyte infiltration with endothelial proliferation in the included capillaries.

The diagnosis of leukemia rests on the presence of typical myeloid infiltration of the liver and spleen, the marked splenomegaly, and the presence of myelocytes in the larger vessel lumina. Mobilization into the circulation does not appear to have been very great at the time of death, but some grade of myelocythemia was present.

In concluding I wish to acknowledge my indebtedness to Drs. Smith and Earle of the Division of Pharmacology for the material and gross notes.

Summary

A case of mast myelocyte leukemia in a cat is reported. Of some twelve reported or mentioned cases of leukemia in cats this is the fourth to be recorded as splenic or myelogenous and the first in cats in which basophilic myelocytes have been the predominating cell type. About nine other cases of mast myelocyte leukemia have been reported in man.

Anatomically this case presented an enormous enlargement of the spleen, enlargement of the liver and extensive mast myelocyte infiltration of the splenic pulp, mast myelocyte nodules in the liver and distention of liver capillaries by blood and large numbers of mast myelocytes. Numbers of mast myelocytes were seen in hepatic and renal veins. The blood, lymph glands and bone marrow were not examined.

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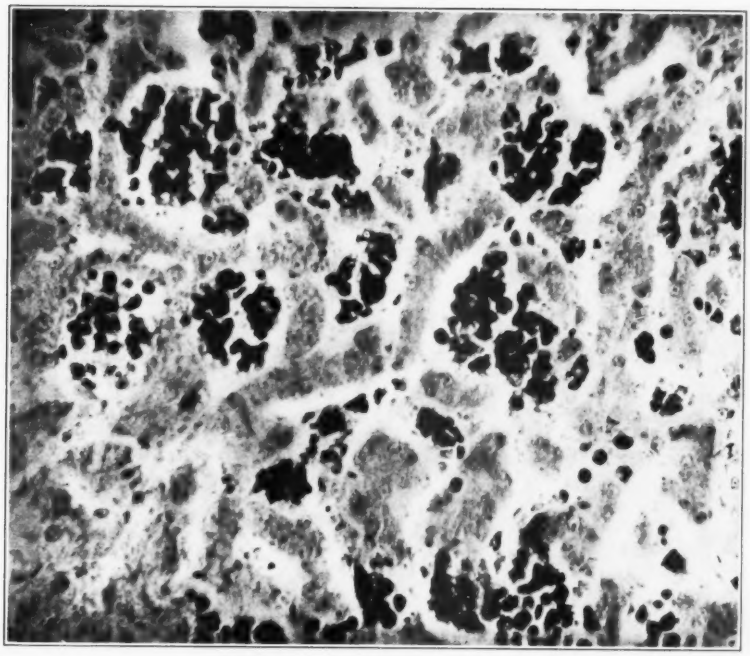
DESCRIPTION OF PLATES

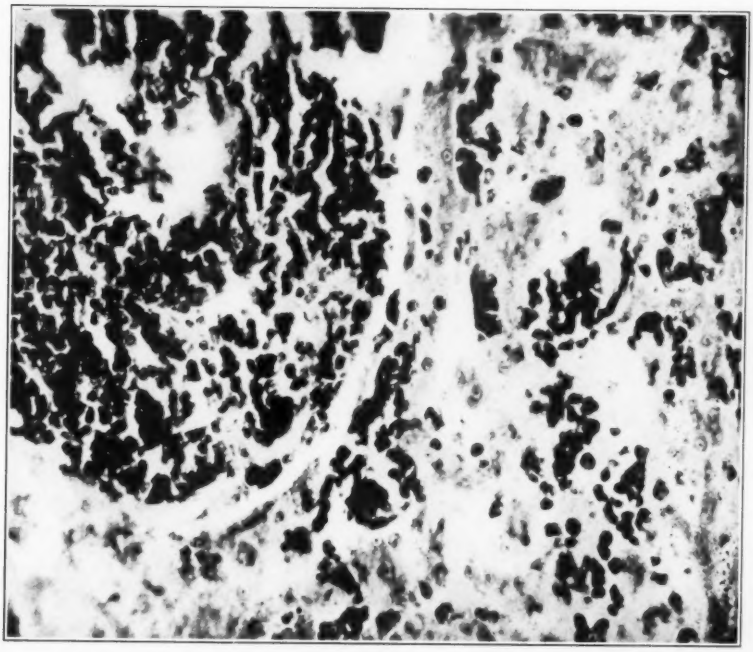
PLATE 154

FIG. 1. Liver. Giemsa stain. E filter. × 300.

FIG. 2. Liver, periportal nodule. Giemsa stain. E filter. × 300.



1



2

Lillie

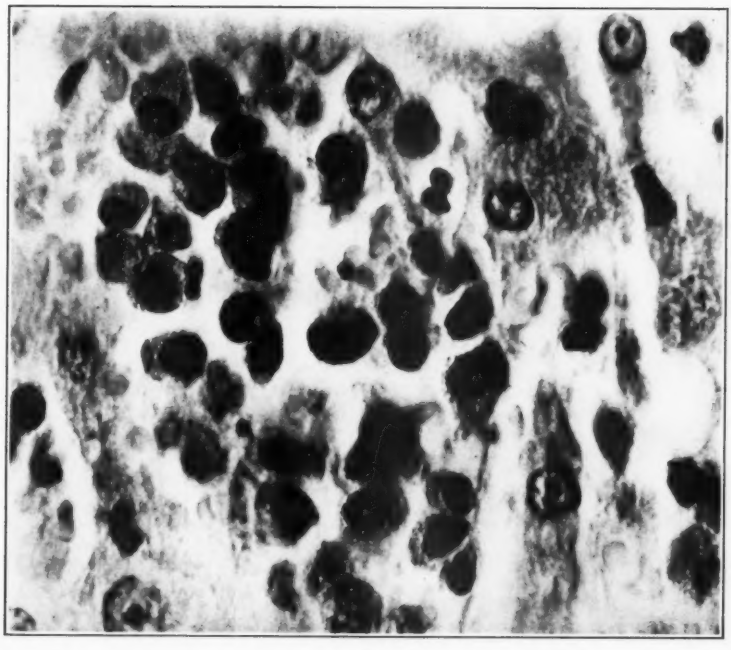
Mast Myelocyte Leukemia in a Cat

PLATE 155

FIG. 3. Liver, vein. Iron chloride hematoxylin and safranin stain. K-1 filter. × 400.

FIG. 4. Liver. Iron chloride hematoxylin and safranin stain. K-1 filter. × 1200.

3

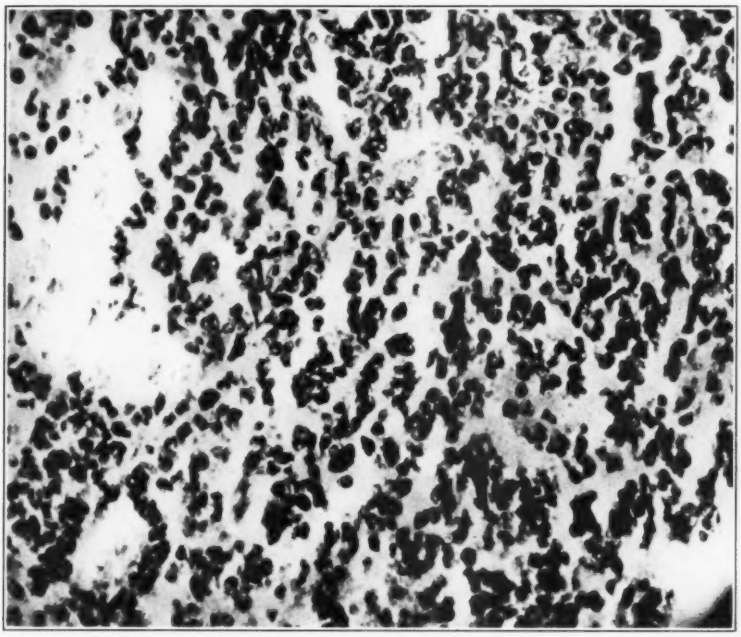


4

PLATE 156

FIG. 5. Spleen. Giemsa stain. E filter. × 300.

FIG. 6. Spleen. Iron chloride hematoxylin and safranin stain. K-1 filter. × 1200.



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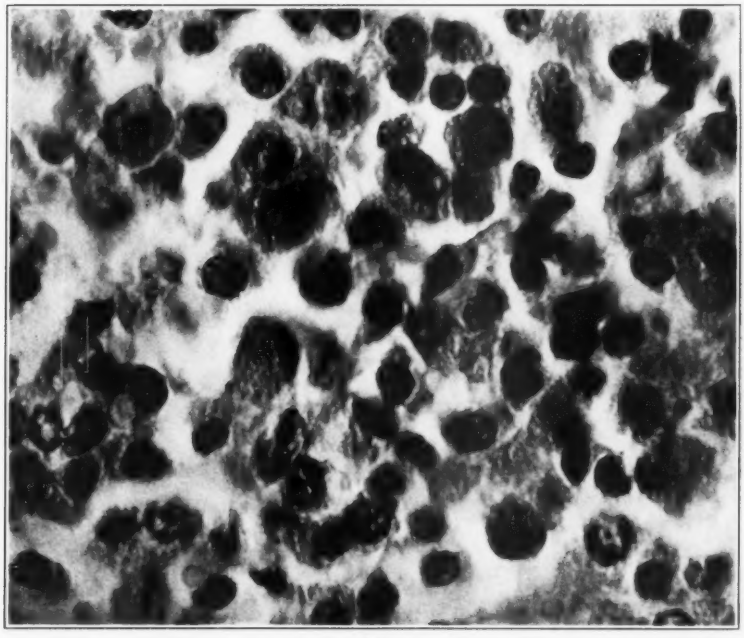

6

TUMORS OF THE ISLANDS OF LANGERHANS AND HYPOGLYCEMIA *

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Pancreatic adenomas of island tissue are not as rare as the small number of reported cases would lead one to believe. In 1926 Warren [1] reported the occurrence of four such cases in the autopsy material which he studied, although he could find only sixteen reported in the literature up to that time. In Warren's report these tumors were characterized by resemblance to the islands in the arrangement and appearance of the cells, by an absence of mitotic figures, by the presence of a definite capsule and by compression of the adjacent tissue. He mentions in only one case the presence of granules characteristic of island cells. In this instance only beta granules were demonstrated. In the cases reviewed by Warren, diabetes occurred in one instance.

Gruber [2] calls attention to a case reported by Walz as a basal cell tumor of the pancreas. This tumor Gruber believes was an island cell adenoma. Two points about this case are of special interest: the patient was a diabetic and had also a carcinoma of the liver associated with cirrhosis.

Since Wilder's report [3] of an island cell carcinoma with hypoglycemia, one other case of adenoma without clinical symptoms of hypoglycemia has been reported by Lloyd.[4] This was a case with an adenoma of the hypophysis and tumor-like enlargements of the parathyroids and islands of Langerhans.

Previous to 1927 a number of authors discussed the possibility of certain carcinomas of the pancreas originating in island tissue, but this origin was never conclusively proved in any of the cases reported.

In 1927 Wilder published his remarkable case of carcinoma of the islands of Langerhans with hypoglycemia. Up to this time the literature contained no mention of the clinical correlation between

* Received for publication May 1, 1931.

tumors of the island cells and hypoglycemia, although Harris [5] had previously called attention to cases with clinical symptoms of unexplained hypoglycemia. Wilder's patient was a physician who required hourly doses of glucose to prevent convulsions from spontaneous hypoglycemia. When ingestion of the necessary sugar was delayed, the blood sugar fell below 0.03 per cent. An autopsy revealed a carcinoma of the pancreas with metastases to the liver and lymph nodes. The cells of the pancreatic tumor bore a striking resemblance to the cells of the islands of Langerhans, and alcoholic extracts made from the metastatic tissue in the liver acted like insulin when injected into rabbits. The granules characteristic of island cells could not be demonstrated, perhaps because of improper fixation.

In 1928 Thalhimer and Murphy [6] reported a similar case in which symptoms continued with increasing severity for two and a half years, until the patient developed a state of almost constant semistupor, accompanied by frequent convulsions and marked hypoglycemia. Death occurred apparently from exhaustion. At autopsy the only significant pathological finding was a small tumor of the pancreas measuring 1.5 by 1 cm. Its microscopic appearance indicated that it originated from the cells of the islands of Langerhans, and it was called a carcinoma of low grade malignancy or an adenoma. The tissue was improperly fixed for staining cell granules, but Bensley was successful in demonstrating dust-like granules which stained very feebly in some of the tumor cells.

In 1929 Howland, Campbell, Maltby, and Robinson [7] reported another case which was successfully operated upon. In this patient dysinsulinism had existed for a period of six years, with attacks of coma and convulsions increasing in frequency. These attacks could be warded off by the administration of food and were found to be associated with low blood sugar levels. At operation a tumor measuring 1.5 cm. in diameter was found in the middle of the pancreas. This was removed. It was called a slowly growing carcinoma of island tissue. At the time of operation, search was made for possible metastases but none were found. The patient recovered and has since been entirely free from attacks. This was the only reported case successfully treated by removal of the tumor up to 1930.

In 1928 McClenahan and Norris [8] reported a case with periodic attacks of loss of memory and loss of consciousness with hypo-

glycemia. At autopsy there was found a large circumscribed adenoma of island tissue, together with hypertrophied islands in the remainder of the pancreas. This is the only one of these four cases associated with hypoglycemia in which the author made a definite diagnosis of benign tumor, but in two of the other cases the tumor, although called a carcinoma, was said to be very slowly growing. This is also the only one of the four cases in which the other islands in the pancreas were considered hypertrophied. The tissue, again, was improperly fixed for staining cell granules.

During the past year and a half we have observed at autopsy three cases of adenoma of the islands of Langerhans, one with a clinical history of hypoglycemia (Case 1), one with no clinical symptoms referable to the pancreas (Case 2), and one with mild diabetes (Case 5). In addition, we have seen surgical material from a case with hypoglycemia which was recently successfully operated upon at Barnes Hospital (Case 3),* and material from an autopsy performed by Dr. Rabinovitch at the Missouri Baptist Hospital (Case 4).

Case Reports

Case 1. (Autopsy No. 4120.) [*Clinical History:* The patient, an electrician aged 40 years, was first admitted to the hospital February 3, 1925, with the chief complaint of dizziness and a dull aching headache in the back of his head. This had begun two years previously. He had had one attack of unconsciousness.] The patient's past history showed the usual diseases of childhood. At 14 and 18 years of age he had chills and fever following gonococcal infections, and, at the age of 20 years, a chancre treated by cautery. The blood Wassermann taken at 28, 33, and 35 years of age was negative.

[On physical examination the pupils were irregular, sluggish to light, but active to distant accommodation. The reflexes were all hyperactive. The blood Wassermann was negative. The spinal fluid showed a Wasserman ++++,] 26 lymphocytes, Pandy +++, and a colloidal gold curve 2225532100. The patient entered the hospital for a lumbar puncture, which was done with no untoward symptoms.

In June 1926 the patient was again admitted for a lumbar puncture. The physical signs were essentially as above. [There was no evidence of posterior column or pyamidal tract lesions. He had improved steadily under treatment with neosalvarsan and tryparsemide and mercury injections.] The blood Wassermann and Kahn reaction were negative as before. The spinal fluid Wassermann was now negative and the Pandy ++.

* Another case of adenoma of the islands of Langerhans recently operated upon at the Peter Bent Brigham Hospital is referred to by Warren in a footnote (page 182) in his book, The Pathology of Diabetes Mellitus. Since the writing of this paper, a second case has been successfully operated upon at Barnes Hospital. This case is to be reported by Dr. Nathan Womack.

He was admitted a third time for a lumbar puncture, March, 1927. Since the second admission he had had ten to fifteen mild dizzy spells. On several occasions he had loss of consciousness, and on one occasion he had fallen. The physical findings were about the same as on the two previous admissions. At this time a brain tumor of the right frontal lobe was considered. The stereoscopic films of the skull were indeterminate and the evidence was considered insufficient to warrant an exploratory operation. The laboratory findings on this admission were: spinal fluid 2 lymphocytes; Wassermann negative; colloidal gold curve 12222100000; urine negative, phenolsulphonephthalein 21 per cent in two hours.

In October, 1927 the patient was admitted for the fourth time as an emergency, having recently become stuporous and irrational. An intracranial lesion seemed possible. At times he would spontaneously open his eyes, look at one with a silly grin, turn over on his side, and fold his arms about his head. At this time while stuporous, he had a bilateral ankle clonus but no abnormal toe signs. Later, while he was still in a stupor, he had both a bilateral Babinski and an ankle clonus, but the next day, October 4, when the patient was no longer stuporous but rather alert, the ankle clonus had disappeared and the Babinski remained positive only on the right side. October 5 the Babinski on the right side was considered doubtful. At this time positive signs of a brain tumor were again considered insufficient for operation. The spinal fluid and the blood Wassermann were still negative. He improved without specific treatment and was discharged October 12, 1927.

October 25th, 1928 he reëntered for a lumbar puncture, his fifth admission. There had been practically no specific treatment for the past year, but he had improved somewhat. The patient thought his speech was slower than formerly and that his mental ability had decreased. He appeared emotionally unstable. The physical signs were essentially as on the first admission. There were no abnormal toe signs and no ankle clonus. A lumbar puncture showed a fluid with a negative Kahn and Wassermann reaction, a colloidal gold curve of 444552000, and 4 lymphocytes. The phenolsulphonephthalein was 35 per cent in two hours.

The patient's final and sixth entry was on June 7, 1930, when he was sent into the hospital as an emergency case. He was unconscious and practically in shock, and had been brought from Topeka, Kansas in this condition. The history obtained from his wife disclosed that he had had occasional spells of unconsciousness for the past three months. These attacks had begun with weakness of legs, numbness of hands and mental confusion. Eventually he would fall and remain unconscious from one to twelve hours. During these attacks he had shown a marked emotional disturbance, laughing foolishly, making peculiar grimaces, kicking his feet in the air and jumping in and out of bed. The present period of unconsciousness had begun two days before entry.

On admission he was comatose. The skin was cold and clammy. There was marked dehydration and there were coarse râles throughout the chest. The pupils were unequal and sluggish. There was a left facial weakness and a bilateral Babinski. The laboratory findings were: red blood count 6,000,000; hemoglobin 90 per cent; white blood count 19,700; blood Wassermann and Kahn negative; spinal fluid Wassermann and Kahn negative; colloidal gold curve 0012210000; Pandy ++; one lymphocyte. Urine negative; blood nonprotein nitrogen normal. Blood sugar 58 mg. per 100 cc. of blood. His temperature rose rapidly to 39 C and signs of pneumonia developed in the left

lower lobe. A blood culture was positive for *Streptococcus viridans*. The temperature rose rapidly on June 10 and the patient died early the following morning. The temperature just before death was 41.8 C.

In brief, the patient, a white male 40 years of age with a definite history of syphilis and having on one occasion a four plus spinal fluid Wassermann, complained of peculiar attacks of dizziness and unconsciousness over a period of five years. At first these attacks appeared infrequently. Later they increased in frequency and lasted from one to twelve hours. Signs of an anatomical lesion in the central nervous system were transient and variable. On the final admission, the patient had been unconscious for two days and remained unconscious for four days in the hospital, when he died from pneumonia.

The laboratory report of the blood sugar determination was not returned until after the autopsy report was made.

Anatomical Findings in Brief

The body is that of a well nourished male adult of 40 years, weighing 75 kilos and measuring 175 cm. in length. Rigor mortis has not developed. There is no adema. On the right ankle and foot there is a skin lesion which resembles impetigo contagiosa. Pupils are equal and regular.

The heart, aorta, spleen, stomach and intestines are normal. With the exception of the pancreas, the glands of internal secretion are normal.

The lungs are covered with a smooth and glistening pleura. The left lower lobe feels non-crepitant. On section the cut surface of this lobe shows areas which are red and consolidated. These areas have a patchy distribution throughout the lobe. Considerable fluid oozes from both lungs. The bronchi and trachea show no changes.

The liver weighs 1420 gm. and measures 20 by 10 by 7.5 cm. Its capsular surface is rough and uneven, due to projections of small irregular nodules of liver tissue above intervening connective tissue scars. On cut section there is a marked increase in connective tissue separating irregular nodules of liver tissue.

The pancreas weighs 80 gm. and measures 19 by 4 by 2 cm. It appears perfectly normal, perhaps a little smaller than usual. No nodules or irregular firm areas can be felt. On section there is seen

in the center of the head a round circumscribed nodule 1 cm. in diameter. This nodule is a little more vascular than the surrounding tissue. It is not divided into the normal pancreatic lobules, but seems almost homogeneous in structure. Its color is gray, in contrast to the yellowish gray color of the rest of the organ.

No abnormalities are seen when the skull is opened. The brain shows normal convolutions and the meninges are everywhere thin and transparent. The blood vessels, including those at the base of the brain and in the meninges, seem entirely normal. When the brain is sectioned, no gross abnormalities are found.

Microscopic Examination

Lung: There is an extensive polymorphonuclear exudate throughout all the sections examined.

Kidney: The tubular epithelium shows slight cloudy swelling.

Liver: There is an abundance of connective tissue about the portal spaces. This extends out into the liver lobules dividing the liver tissue irregularly. There are many mononuclear cells in this connective tissue and new-formed bile ducts are frequent. There has been little proliferation of liver cells.

Brain: Several sections show no changes in the brain itself. The meninges are quite normal. The small blood vessels in the brain substance and in the meninges are normal. There is no cellular infiltration about vessels either in the brain or in the meninges.

With the exception of the pancreas other organs shows no microscopic abnormalities.

Pancreas: The pancreas, at a distance from the tumor, shows a slight increase in interlobular connective tissue. In another section the tumor nodule is irregular in outline, but everywhere is sharply demarcated from the surrounding pancreatic tissue. Throughout most of its circumference it is surrounded by a fairly thick connective tissue capsule, but in a few places it is separated from the normal pancreatic tissue only by a very thin strand of connective tissue, scarcely more than the capsule about a normal island. The tissue about the tumor nodule is compressed here and there, and there is more scarring in this region than elsewhere in the pancreas. Normal islands are seen near the tumor, but never continuous with it. In the nodule there are strands and masses of cells divided by an inter-

lacing connective tissue stroma that is almost acellular and has a homogeneous hyaline character. Capillaries are fairly numerous in this connective tissue. The tumor cells often border the capillaries. The peculiar connective tissue stroma suggests a resemblance to the hyaline tissue seen in the so-called hyaline islands. The tumor cells all stain alike with hematoxylin and eosin. They have an abundance of cytoplasm which stains with eosin like the cytoplasm of island cells, in contrast to the more basophilic cytoplasm of acinar cells. The nuclei are round or slightly oval. They are much like those of normal island cells.

In a section of pancreas fixed immediately at autopsy in Zenker-formol the cells of the normal islands have a normal content of beta granules when stained with Bensley's neutral gentian or Bowie's stain. Alpha granules do not stain. Material from the tumor was not fixed until later, so that the granular content of the cells is poorly preserved, but one can find individual cells in the tumor which show a few of the characteristic small blue beta granules which stain with Bensley's neutral gentian or Bowie's stain. This seems to prove beyond doubt that the tumor is derived from island tissue and that at least a part of the cells contain beta granules. The material is such that a detailed study is not possible.

Anatomical Diagnoses: Pancreatic adenoma of island tissue; cirrhosis of liver; bronchopneumonia; impetigo contagiosa of right foot.

Comment

The periodic attacks of dizziness, loss of consciousness and coma, with the peculiar emotional reactions which this patient experienced over the period of observation, are explained by a functioning tumor of the islands of Langerhans. There is a record of only one blood sugar determination, but this one determination showed a definite hypoglycemia. This case is of special clinical interest because of the obscuring influence of a suspected central nervous system lesion. The laboratory evidence of syphilis of the central nervous system at the beginning of this man's history colored the interpretation of the clinical symptoms throughout the course of his illness. Yet these clinical symptoms were so atypical of syphilis that a diagnosis of brain tumor involving the frontal lobe was also seriously considered. When one considers the descriptions of the

attacks, comparing them with the descriptions in previous reports, they seem quite characteristic of hypoglycemic manifestations. In all of the reported cases the attacks have been similar. Besides the actual coma and convulsions there are certain characteristic symptoms which are mentioned repeatedly: the mental daze and loss of memory, peculiar grimaces, aimless movements of arms and legs, and the display of an amiable or even jocular mood when aroused from stupor. Profuse perspiration at the termination of attacks is common.

The small size of this tumor, together with the fact that it did not contrast sharply with the normal pancreatic tissue shows the possibility of overlooking such a tumor even at autopsy.

In this connection a case such as that reported by Finney and Finney [9] is of interest. Their patient, a woman aged 53 years, with a psychopathic background, had hysterical attacks with stupor and unconsciousness associated with a low blood sugar. An operation was performed. As no tumor was discovered the operators removed a large part (22.5 gm.) of the normal pancreas. The patient recovered from the operation. The blood sugar, although somewhat higher than previously, continued abnormally low. The symptomatic attacks were believed to be lessened in frequency and severity, but were still of a character to incapacitate the patient. It seems not unlikely that a tumor of small size remained undiscovered in the part of the pancreas not removed.

Likewise two cases operated upon at the Mayo Clinic and one operated upon by Holman, all referred to by Allan, *et al.*,[10] have shown similar courses with slight but unsatisfactory improvement. In each of these three cases no tumor was found at operation and a part of the normal pancreas was removed.

That such cases represent hypertrophy or hyperfunction of normal islands, or even some abnormality outside the pancreas, rather than an undiscovered tumor is, of course, possible. But, realizing how indistinct an adenoma may be even at autopsy, one is left in doubt as to the absence of a tumor in such cases.

Two of the other adenomas which we have seen help to explain the nature of these tumors.

CASE 2. (Autopsy No. 3950.) In this instance the adenoma was an incidental finding at autopsy in a man dying from a primary liver cell carcinoma. After the discovery of the pancreatic tumor a careful

inquiry was made into the man's history taken in the hospital where he was under observation for six weeks before his death. Not the slightest clinical evidence of hypoglycemia was recorded. Unfortunately no blood sugar determination had been made.

This adenoma was located near the middle of the body of the pancreas. It was of approximately the same size as that in Case 1, in which hypoglycemia was demonstrated. The tumor was recognized grossly, when the pancreas was sectioned, by its gray color which contrasted with the yellowish gray color of the surrounding pancreatic tissue, and by its lack of normal pancreatic lobules. Grossly it showed no evidence of increased vascularity.

Microscopically, with a hematoxylin and eosin stain, one finds a tumor nodule surrounded by a rather thick capsule of connective tissue. This capsule completely surrounds the nodule, but in places there are islands of tumor tissue in the capsule in very close contact with the normal pancreatic tissue. In other places normal islands and a few acini are seen within the capsule and bands of connective tissue extend into the tumor from the capsule. The pancreatic tissue outside this capsule shows a moderate amount of interacinar scarring. A few acini are distended and contain a little colloid-like material. The tumor cells are arranged in interlacing bands and small clusters. In some areas they seem less well preserved and have no definite arrangement but form a group of isolated cells. In such places the cells stain a little more intensely with eosin than in the rest of the tumor. Between the columns of cells there is a conspicuous homogeneous connective tissue stroma, much like that described in Case 1, but even more conspicuous. The capillary channels are sometimes quite wide and filled with blood. The individual cells in this tumor resemble island cells. They are of about the same size. Their cytoplasm is eosinophilic rather than basophilic like that of the acinar cells, but the nuclei are on the whole somewhat smaller than those of the normal island cells and the chromatin material is denser. The islands near the tumor and in another section taken at a distance from the tumor are not abnormal in size.

With Bowie's stain, following Zenker-formol fixation, the cells in the normal islands show a normal content of beta granules, but alpha granules are not recognized. In the tumor, however, many of the cells contain small indistinct granules which take a reddish stain. In other cells a few normal beta granules occur mixed with the red-

dish granules, while still other cells are filled with beta granules like those of the beta cells of normal islands. The beta granules are frequently arranged at one pole of the cell. With no other material to help in the interpretation of this case, we might have come to the conclusion that this tumor was composed only in part of beta cells with a large number of cells which were probably alpha cells. A similar appearance is described by Robinson in the case reported by Howland, Campbell, Maltby and Robinson and is interpreted by Robinson as indicating the presence of both alpha and beta cells in the tumor, sometimes both alpha and beta granules occurring in the same cells. Fortunately very fresh surgical material from a patient (Case 3) operated upon by Dr. A. O. Fisher and reported by Carr, *et al.*,[11] was studied here by Bensley, and throws light on the character of these cells.

CASE 3. This patient, a young boy, had shown characteristic symptoms of hypoglycemia for at least one and a half years. The tumor removed from the body of the pancreas measured 2 by 1.5 cm. When fixed in Zenker-formol this surgical material stained much like the material just described (Case 2, Autopsy 3950), but fewer tumor cells were seen containing normal beta granules. A few normal islands in the attached pancreatic tissue showed a normal content of beta cells, but Bensley also fixed material in acetic-osmic-bichromate mixture and stained it with acid fuchsin-picric acid. This method which stains alpha granules well, failed to demonstrate them in the tumor cells. Fresh tissue treated with neutral red showed many cells of the tumor packed with granules taking up the neutral red dye, a characteristic of beta as well as alpha cells, while other cells contained small granules which did not seem to take up the dye. This fact, he believed, showed that the unusual cells in the tumor were not alpha cells but modified beta cells, a condition which one might expect in tumor tissue.

CASE 4. This case adds nothing more to our knowledge of the character of these tumors but helps to emphasize their frequency. The tumor was also an incidental finding at autopsy and the material was not ideally fixed, although it was possible to stain beta granules in some cells of the tumor and in some normal island cells with Bowie's stain. It measured only 6 mm. in diameter. Microscopically, with hematoxylin and eosin, the tumor although small closely

resembles the surgical material in Case 3. The history of the patient is vague. He was a man 50 years of age, operated upon for intestinal obstruction because of symptoms of vomiting and abdominal pain. No obstruction was found but a gall-bladder filled with stones. He died following the operation. No satisfactory cause for the clinical symptoms or for his death was found at autopsy. Inquiring into the history, after the finding of the small pancreatic adenoma, the interesting information was gained that his family considered the man mentally defective, because of periods of loss of memory.

CASE 5. This case differs from the other four both in the clinical history and in the character of the tumor. This patient was a colored woman of 48 years, who entered the hospital during the course of an acute lobar pneumonia. Several days after the crisis of the disease she died suddenly of a pulmonary embolus which originated in the femoral vein. Her past history gave no record of symptoms referable to a pancreatic lesion, but during the course of this acute infection she behaved as a total diabetic.

At autopsy, the anatomical findings were briefly as follows: resolving lobar pneumonia; extremely large multiple myomata uteri; cardiac hypertrophy; chronic passive congestion of viscera; thrombosis of left iliac and femoral veins; pulmonary embolus; adenoma of islands of Langerhans; cavernous hemangioma of liver.

Only the pancreatic lesions are of interest to us here. Grossly, the pancreas is slightly smaller than usual, weighing only 80 gm. A well encapsulated nodule, measuring 1 cm. in diameter, is seen near the center of the body of the pancreas on its anterior surface. This nodule is paler than the rest of the organ and does not show the regular lobulations of the normal tissue. It is not more vascular than the surrounding pancreas.

In a microscopic section which includes the nodule, the pancreatic tissue shows a slight interacinar and interlobular scarring. An occasional acinus shows some distention of its central lumen. Most of these are at some distance from the edge of the nodule. The ducts show no evidence of obstruction. The islands of Langerhans are of average size and number. With a hematoxylin and eosin stain they show nothing abnormal. About the nodule there is some compression of the pancreatic lobules and more scarring than elsewhere. The nodule is composed of lobules of tissue separated from the normal

pancreas and often from each other by strands of connective tissue. Pancreatic tissue — acini, ducts and islands — are found in the connective tissue capsule, but are distinctly separated from the tumor tissue. However, at times this separation is by a very thin strand of connective tissue. At one side of the nodule there are two large ducts. The wall of one of these is encroached upon by the tumor, so that a mass of the tumor tissue bulges into the lumen of the duct and is covered only by a flattened layer of duct epithelium. This apparent invasion of the duct suggests a malignant growth, but elsewhere the arrangement of cells is so regular and the character of the cells so uniform that one hesitates to speak of this as a carcinoma. The arrangement of cells within the lobules is that of island tissue. There are interlacing strands and circles of uniform cuboidal or columnar cells bordering capillaries. No mitoses are seen. The nuclei are slightly smaller than those of the normal island cells. They are all quite similar in size and in staining qualities.

Although their arrangement suggests island tissue, the cells are more regular in size and shape and are more distinctly columnar than island cells. This character, but not the arrangement of cells, suggests the possibility of origin from duct cells, but when stained with mucicarmine the cells do not contain the drops of mucin seen in the duct epithelium.

With Bowie's stain after Zenker-formol and after Zenker-acetic fixation, no granules taking the specific stain are seen in the cells of the tumor, although the cells in the islands show a normal content of stainable granules, and the acinar cells contain zymogen granules. With a modified Mallory connective tissue stain, using aniline acid fuchsin instead of acid fuchsin, no red granules are seen in the tumor cells, although the blue-stained cytoplasm seems distinctly granular. With the fixations used, the possibility of the presence of alpha granules is not entirely eliminated. Certainly no normal beta granules are present and the existence of abnormal beta granules such as those seen in some of the other adenomas is not demonstrated. Only its structure leads one to believe that this tumor is derived from island tissue. We do not believe that it can be interpreted as a hypertrophic island, for Bensley has called attention to a quite different appearance in such islands. In hypertrophied islands produced by experimental obstruction of comparatively long duration he observed that the cells were always packed with normal granules.

This tumor is unlike the others discussed in this paper, in that it gives neither clinical nor anatomical evidence of functional activity. In addition, this is the only case in which a definite although mild diabetes was present.

Discussion

In all our cases there might be a difference of opinion as to whether they should be called adenomas or slowly growing carcinomas. We are inclined to consider them all as adenomas. The more important conclusion seems to be that they are definite tumors and cannot be considered merely as hypertrophied islands.

Only two island tumors associated with hypoglycemia in which the tumor material has been properly fixed for complete cytological studies (the one described by Robinson and the one studied here by Bensley) have shown atypical cells, probably atypical beta cells, although not so interpreted by Robinson. All the cases associated with hypoglycemia, except that reported by McClenahan and Norris, have shown islands of normal size in the remainder of the pancreas. In their case the islands were considered hypertophied. In those instances (Cases 1, 2, and 3 in this report) in which material has been stained to demonstrate granules in the island cells outside the tumor nodule, these cells have shown a normal granular content. The activity of the normal islands, as determined by this cytological method, does not seem to have been depressed by the excess of insulin produced in the tumor. Nor is there evidence in the cases with hypoglycemia, except perhaps in the case of McClenahan and Norris with hypertrophied islands, to show that the normal islands have been abnormally stimulated. The recovery following removal of the tumor in two cases also shows that there was no overstimulation of the normal islands.

This apparent lack of coördination between the tumor and normal islands is probably linked with functional differences between tumor and normal cells. These cells may therefore not respond to the normal mechanism of insulin control. However, the failure to find clinical symptoms in our Case 2 is not explained by such a theory, for there the tumor also contained many of these abnormal cells and was about as large as the tumor in Case 1 which gave symptoms. The lack of blood sugar determinations leaves us in doubt about this case.

In Case 3 the sugar tolerance curve, in addition to the anatomical study, gave no evidence of change in the normal islands. This is not true of all of the cases, however. The sugar tolerance curves in some of the reported cases of hypoglycemia associated with pancreatic tumors have shown what can be interpreted as a low sugar tolerance, that is, the attainment of an unusual high blood sugar level and a slow return to normal. This suggests some depression of the activity of the normal islands, but corresponding anatomical studies of the islands in properly fixed material is lacking in those cases which showed this peculiar type of sugar tolerance curve.

The occurrence of mild diabetes in one of our cases with a nonfunctioning tumor and, also, in two cases of island adenoma reported in the literature, suggests another possible explanation of this low sugar tolerance in the cases with a functioning tumor. Perhaps in both instances the low sugar tolerance is dependent upon some unexplained developmental defect of the pancreatic islands which also accounts for the growth of the adenomas. In those cases with a similar adenoma without definite diabetes, or without a low sugar tolerance, perhaps the same sort of developmental defect has manifested itself only in the occurrence of the adenoma.

Cecil [13] described similar structures, usually in diabetics, which he believed were hypertrophied islands. Although it may, at times, be difficult to distinguish between adenomatous proliferation and hypertrophy, the following facts argue for the occurrence of true island adenomas. It is known that the normal pancreas is capable of producing many times as much insulin as is required, but it is regulated to the needs of the body. The adenomas are not controlled by the normal mechanism governing insulin liberation and may produce hypoglycemia in spite of their small size. The stimulus that produces their increased growth and function does not affect the normal islands in a corresponding manner. The cells in these tumors are not like the normal island cells. In some of the tumors the cells contain abnormal secretory granules. In others, they have no secretory granules taking specific stains, although the island cells have such granules in apparently normal numbers.

Attention should be called to a possible relation between tumors of the liver and island cell adenomas. One of the adenomas reported here was in an individual dying of a primary liver cell carcinoma. In the case of Walz (discussed by Gruber) a primary liver cell carci-

TABLE I

Results of Glucose Tolerance Tests

I

Wilder's Case

120 GM. GLUCOSE		100 GM. GLUCOSE 15 GM. ½ HR. BEFORE ZERO HR.	
Time	*Blood Sugar*	*Time*	*Blood Sugar*
0	68 mg. per 100 cc.	0	85 mg. per 100 cc.
½ hr.	242 mg.	1 hr.	..
1 hr.	283 mg.	2 hr.	214 mg.
2 hr.	223 mg.	2½ hr.	..
3 hr.	70 mg.	3 hr.	31 mg.

II

Finney's Case

AMT. GLUCOSE NOT RECORDED

Time	*Blood Sugar*
½ hr.	192 mg. per 100 cc.
1½ hr.	135 mg.
2½ hr.	112 mg.

Fasting sugar 52 mg. per 100 cc.

III

Hartmann's Case of Hypoglycemia.[12] *Tumor of Islands Suspected but not Proved*

120 GM. GLUCOSE		200 GM. GLUCOSE	
Time	*Blood Sugar*	*Time*	*Blood Sugar*
½ hr.	135 mg. per 100 cc.	0	74 mg. per 100 cc.
1 hr.	166 mg.	2 hr.	242 mg.
2 hr.	216 mg.	3 hr.	140 mg.
3 hr.	100 mg.	4 hr.	66 mg.

Fasting sugar 53 mg. per 100 cc.

IV

Robinson's Case

100 GM. GLUCOSE

Time	*Blood Sugar*
1 hr.	250 mg. per 100 cc.
2 hr.	260 mg.
3 hr.	240 mg.

V

Case III of this Report

155 GM. GLUCOSE		155 GM. GLUCOSE	
Time	*Blood Sugar*	*Time*	*Blood Sugar*
½ hr.	134 mg. per 100 cc.	½ hr.	172 mg. per 100 cc.
1 hr.	132 mg.	1 hr.	183 mg.
2 hr.	135 mg.	2 hr.	123 mg.
3 hr.	102 mg.	3 hr.	60 mg.
Fasting sugar 81 mg. per 100 cc. (first admission)		Fasting sugar 72 mg. per 100 cc. (third admission)	

noma, as well as the pancreatic adenoma was present. Borst (quoted by Ewing [14]) mentions the occurrence of localized hyperplasias of the pancreas and of the liver in the same individual. In light of these observations two reported cases [15,16] of liver cell carcinoma associated with severe hypoglycemia without other gross evidence of hepatic dysfunction are of interest. In these cases no pancreatic tumor was discovered.

Conclusions

From the cases reported in this paper and those found in the literature one may draw the following conclusions:

1. Pancreatic tumors producing hypoglycemia are composed largely of abnormal beta cells.

2. In those cases with hypoglycemia due to a pancreatic tumor of island tissue the normal island cells are not overstimulated.

3. From anatomical studies in these cases there is no evidence that the activity of the normal island cells is depressed, although clinical studies of the sugar tolerance suggest this in some cases.

4. Adenomas resembling islands of Langerhans in their cellular arrangement, which give neither clinical nor anatomical evidence of functional activity, may occur.

5. Adenomas of the islands of Langerhans are not rare; even those with clinical symptoms are surprisingly frequent.

Note: We wish to thank Dr. R. R. Bensley for his helpful advice and criticism.

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DESCRIPTION OF PLATES

PLATE 157

FIG. 1. Longitudinal section showing adenoma of island tissue in the middle of the head of the pancreas (Case 1). × 0.8.

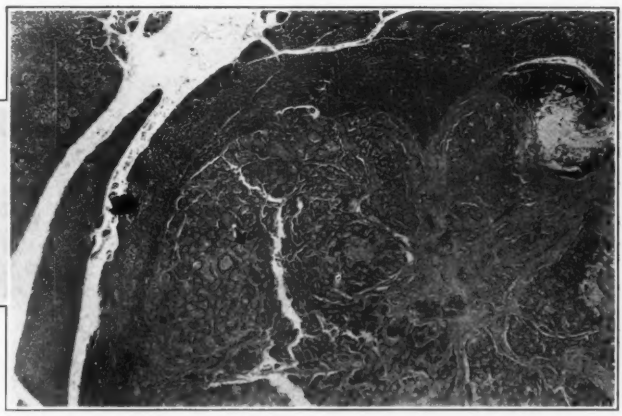
FIG. 2. Cross-section of pancreas showing adenoma of island tissue (Case 2). × 0.8.

FIG. 3. Low power photomicrograph of portion of the adenoma of island tissue shown in Fig. 1 (Case 1).

FIG. 4. Low power photomicrograph of adenoma of island tissue shown in Fig. 2 (Case 2).

1

2



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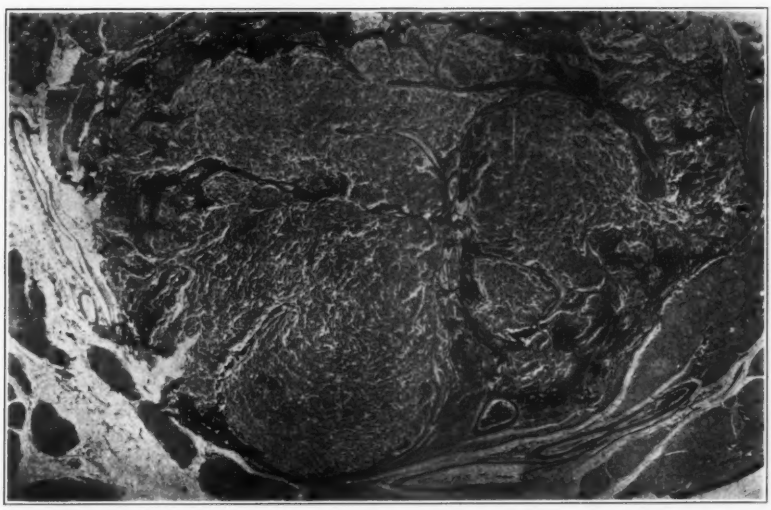


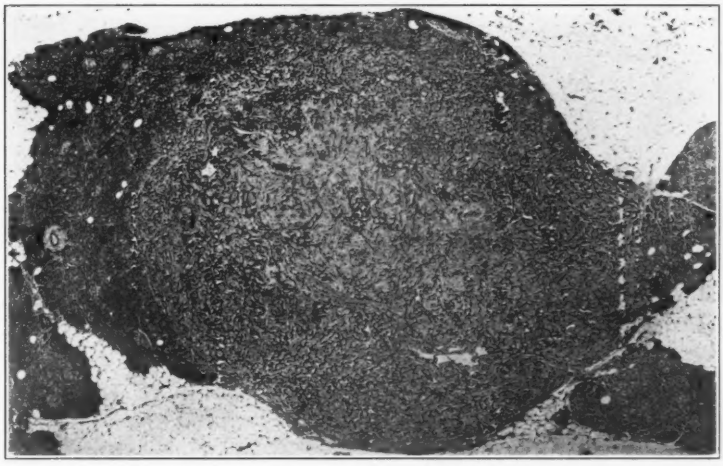
4

Plate 158

Fig. 5. Low power photomicrograph of adenoma of island tissue from Case 4.

Fig. 6. Low power photomicrograph of adenoma of island tissue from Case 5.

Fig. 7. Higher magnification of adenoma shown in Figs. 1 and 3 (Case 1). The hyaline connective tissue between groups of tumor cells is shown. Compressed pancreatic tissue extends between two lobules of the tumor.



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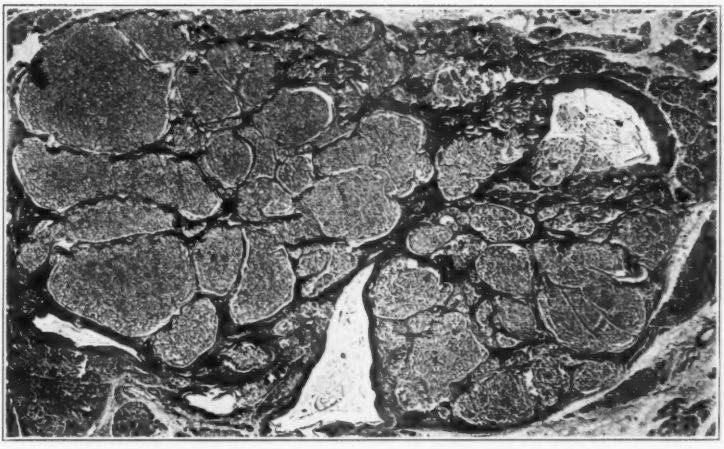

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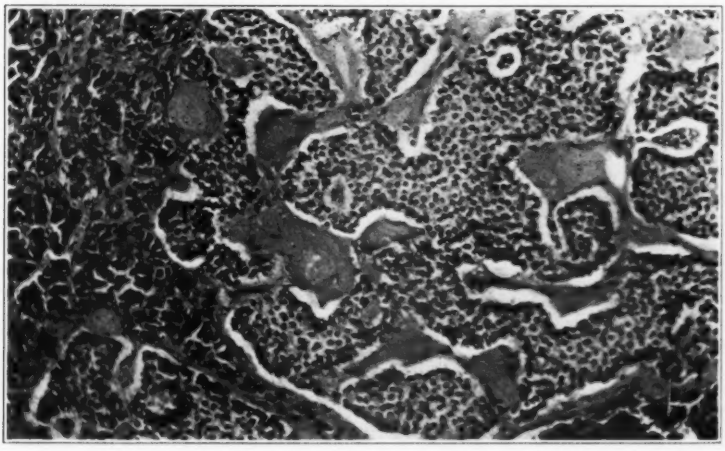

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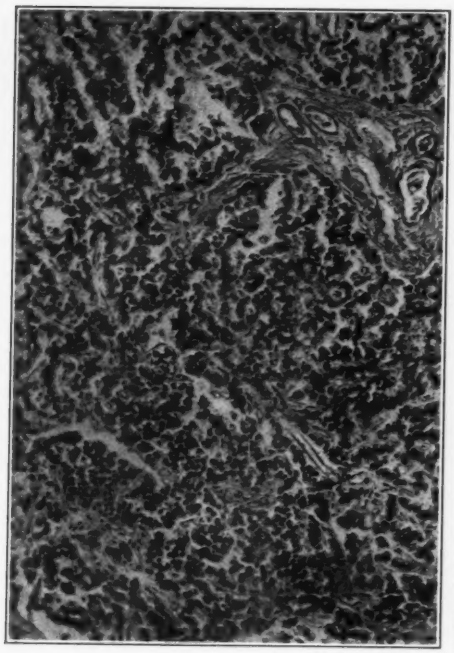
PLATE 159

FIG. 8. Higher magnification of adenoma shown in Figs. 2 and 4 (Case 2). The hyaline connective tissue is seen between strands of tumor cells.

FIG. 9. High power photomicrograph of adenoma of island tissue removed at operation (Case 3). The hyaline connective tissue stroma is conspicuous.

FIG. 10. Higher magnification of adenoma shown in Fig. 5 (Case 4). The connective tissue stroma is again conspicuous.

FIG. 11. Higher magnification of adenoma seen in Fig. 6 (Case 5). The capsule about the tumor is shown. The hyaline connective tissue in the tumor is prominent.



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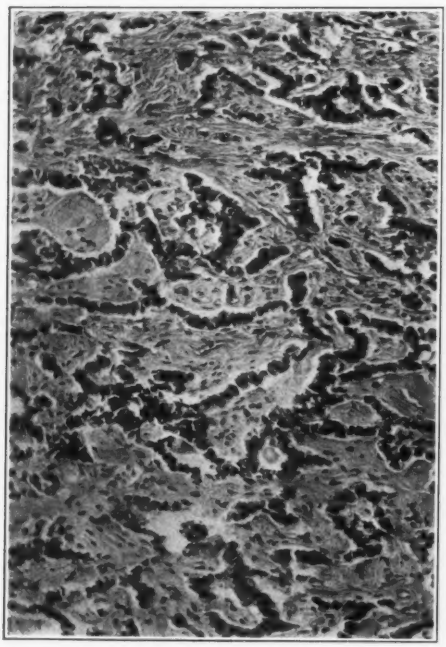

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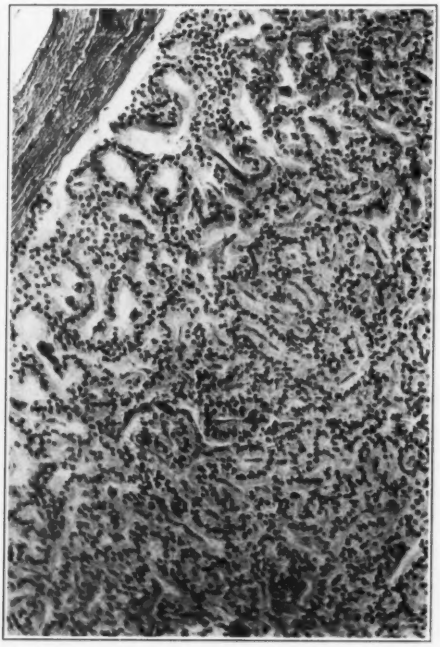

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